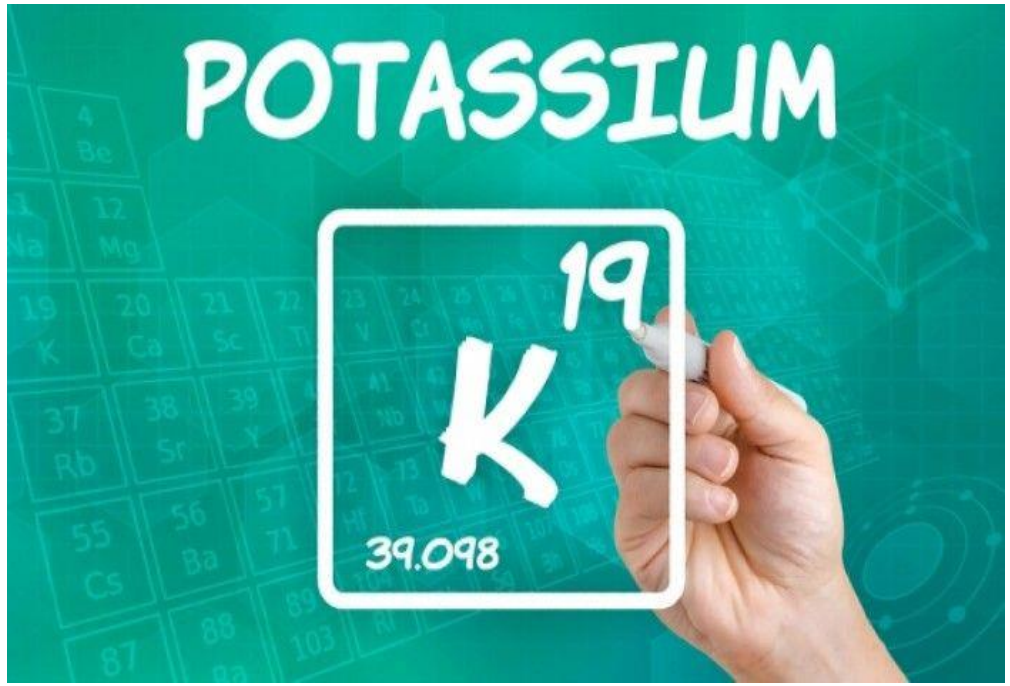
Πώς εφαρμόζονται οι ανανεωμένες κατευθυντήριες οδηγίες για την διαχείριση της υπερκαλιαμίας στην κλινική πράξη;



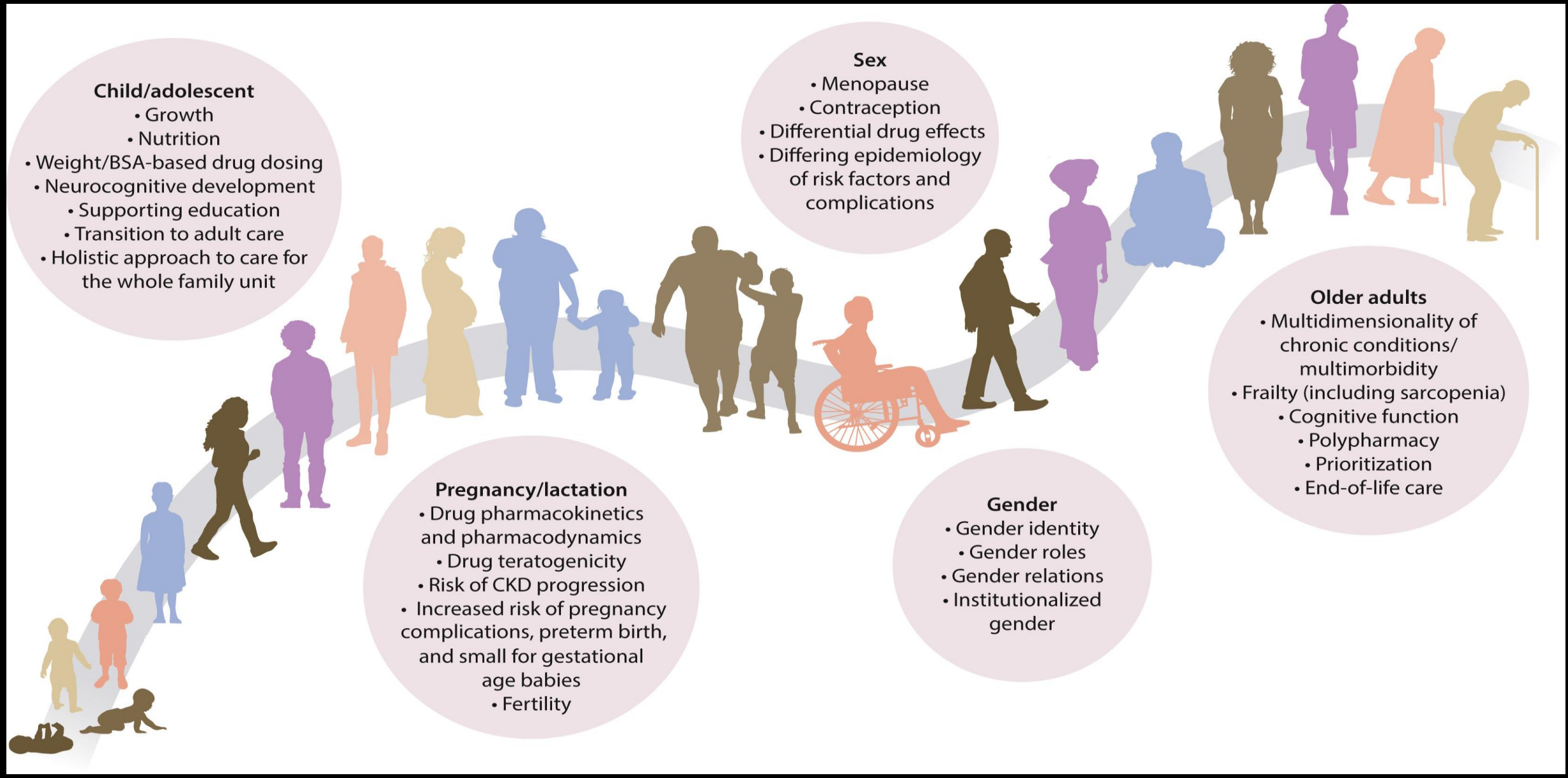
Ι. Γριβέας, MD,PhD

Νεφρολόγος

athens-NEPHROLOGY

Καμία σύγκρουση συμφερόντων

«Οι παρουσιάσεις στοχεύουν σε εκπαιδευτικούς σκοπούς και μόνο, και δεν αντικαθιστούν την ανεξάρτητη επιστημονική κρίση. Οι δηλώσεις και οι απόψεις που εκφράζονται προέρχονται αποκλειστικά από τους ομιλητές και, εκτός από την περίπτωση που δηλώνεται ρητά το αντίθετο, δεν αποτελούν άποψη ή θέση της AstraZeneca. Η AstraZeneca δεν υποστηρίζει, δεν εγκρίνει και δεν αναλαμβάνει καμία ευθύνη για το περιεχόμενο, την ακρίβεια ή την πληρότητα των πληροφοριών που παρουσιάζονται.»



Kidney International 2024 105684-701DOI: (10.1016/j.kint.2023.10.016)

www.kidney-international.org KDIGO executive conclusions

Kidney International (2019) ■, ■–■ A .
j.kint.2019.09.018

. · 1 A

Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

open

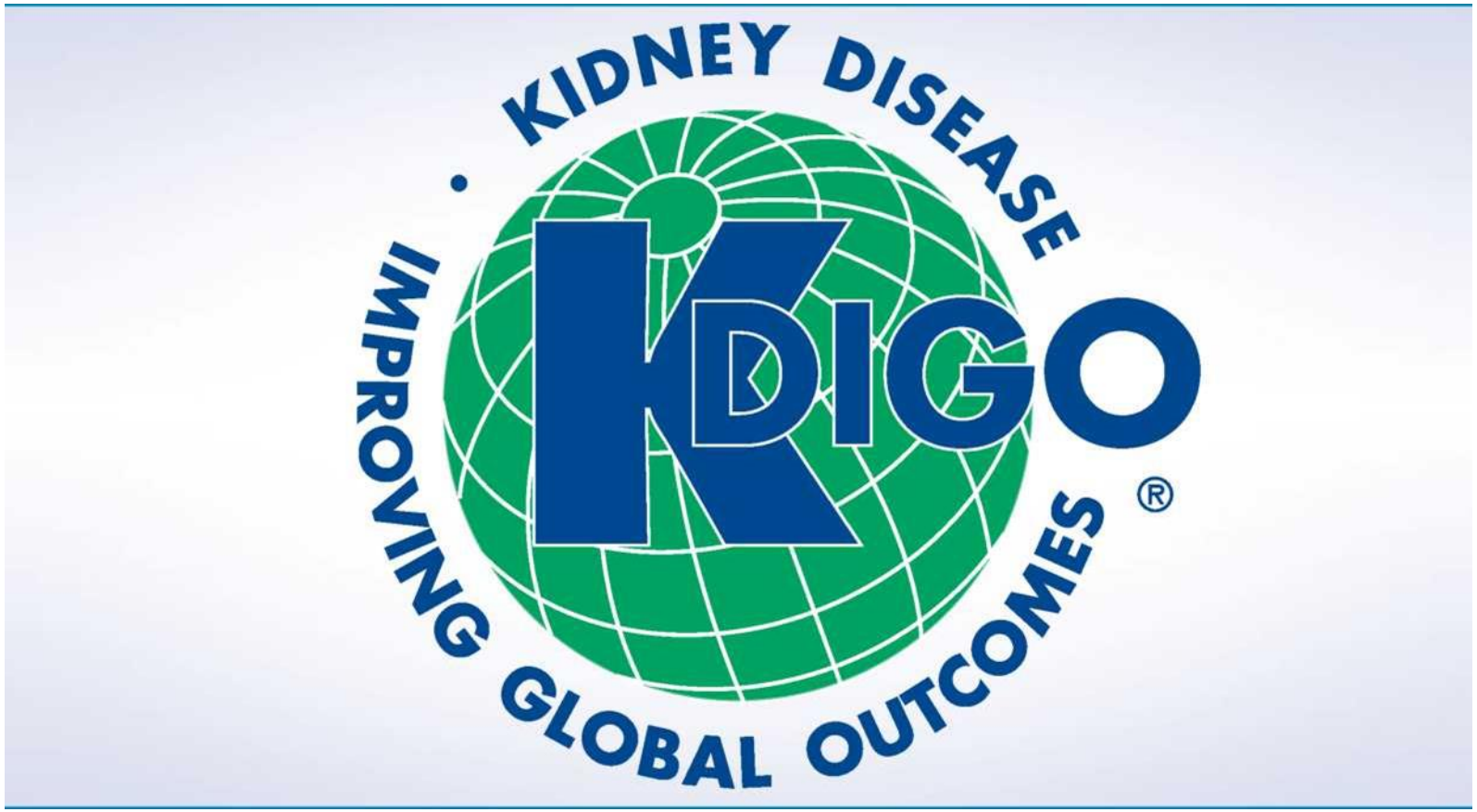
Catherine M. Clase[1,2], Juan-Jesus Carrero[3], David H. Ellison[4], Morgan E. Grams[5,6], Brenda R. Hemmelgam[7'8], Meg J. Jardine[9'10], Csaba P. Kovesdy[11'12], Gregory A. Kline[13], Gregor Lindner[14], Gregorio T. Obrador [5], Biff F. Palmer [6], Michael Cheung[17], David C. Wheeler[18], Wolfgang C

. Winkelmayer[19] and Roberto Pecoits-Filho[20,21]; for Conference Participants[22]

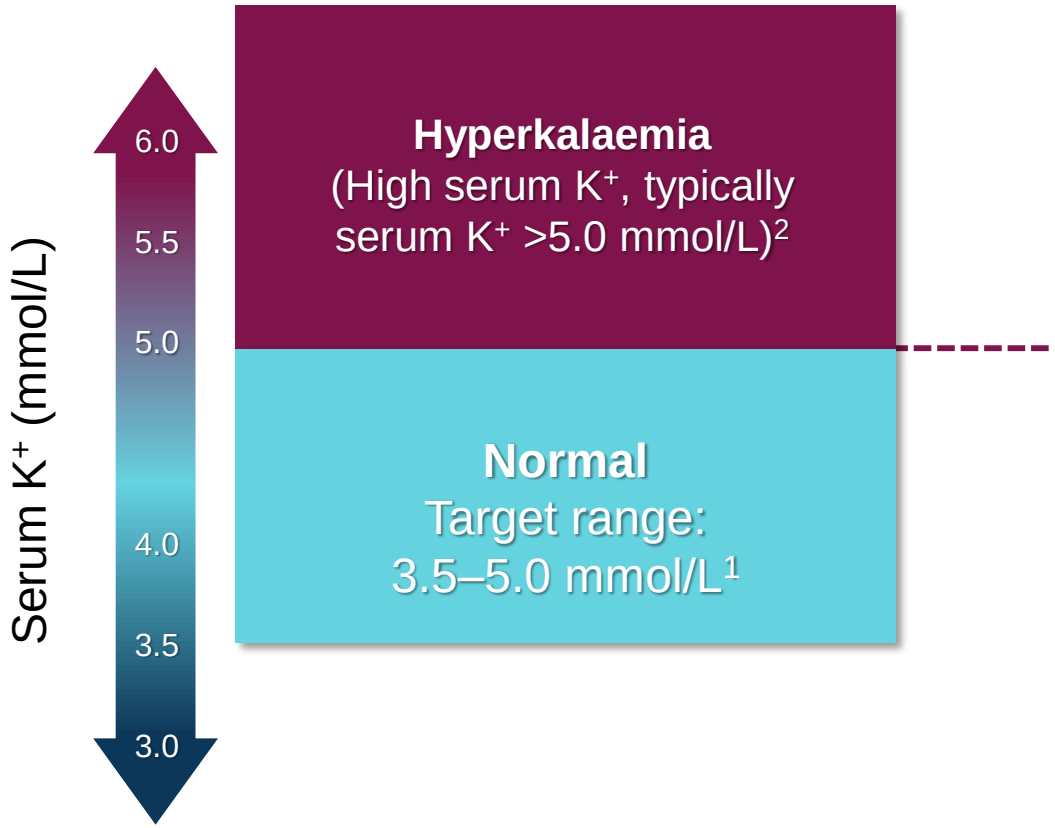
A multidisciplinary group of researchers and clinicians met in October 2018 to identify evidence and address controversies in potassium management. Here we provide our overview of potassium homeostasis in health and disease and guidance for evaluation and management of dyskalemias in die context of kidney diseases, and indicate research priorities.

KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

VOLUME 105 | ISSUE 4S | APRIL 2024
www.kidney-international.org



Normal blood (serum) levels of K^+ are typically 3.5–5.0 mmol/L[1]

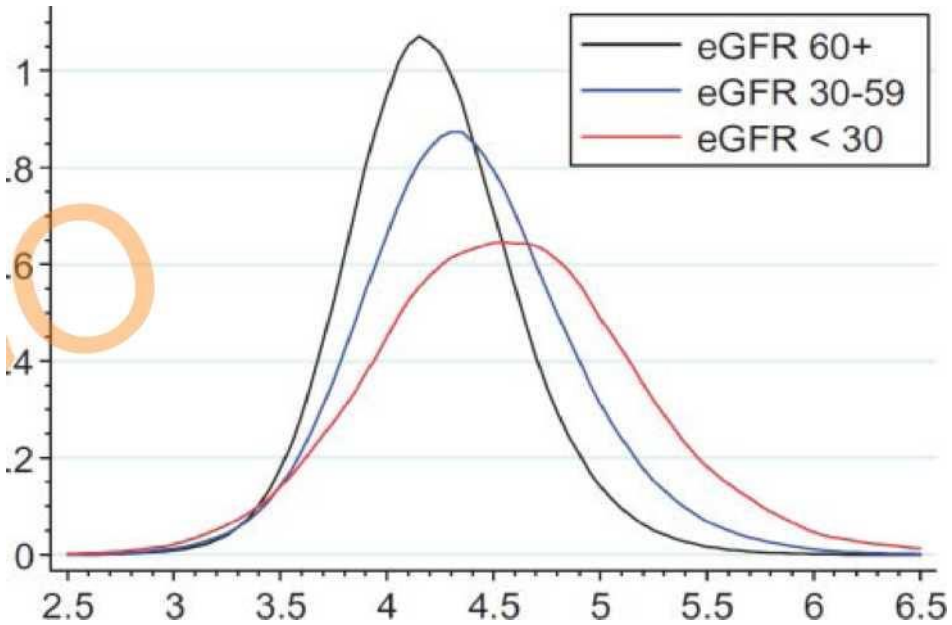


Hyperkalaemia definition varies but is typically serum K^+ **>5.0 mmol/L**[2]

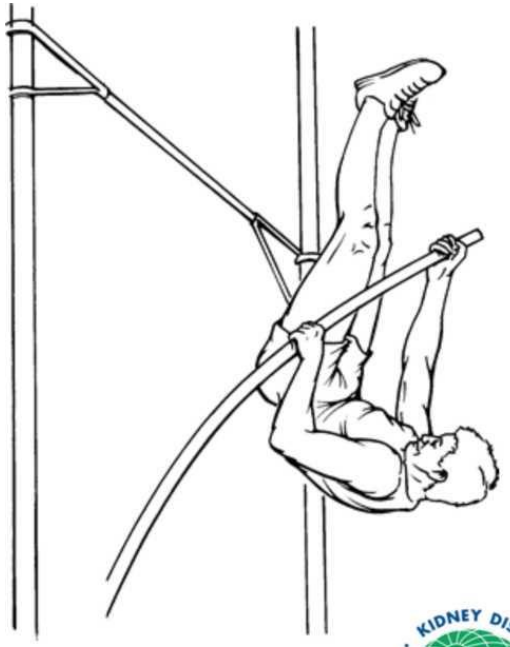
- **>6.0 mmol/L** is considered **severe**
- Symptoms include muscle weakness or numbness and abnormal heart rate

K^+, potassium ion

1. Boron WF & Boulpaep EL. Medical Physiology, 3rd Edition, Elsevier, 2017; 2. Gennari FJ. *Crit Care Clin* 2002;18:273– 288



Gasparini Nephrol Dial Transplant 2018 Kovesdy Eur Heart J 2018



Are you cardiology or nephrology?

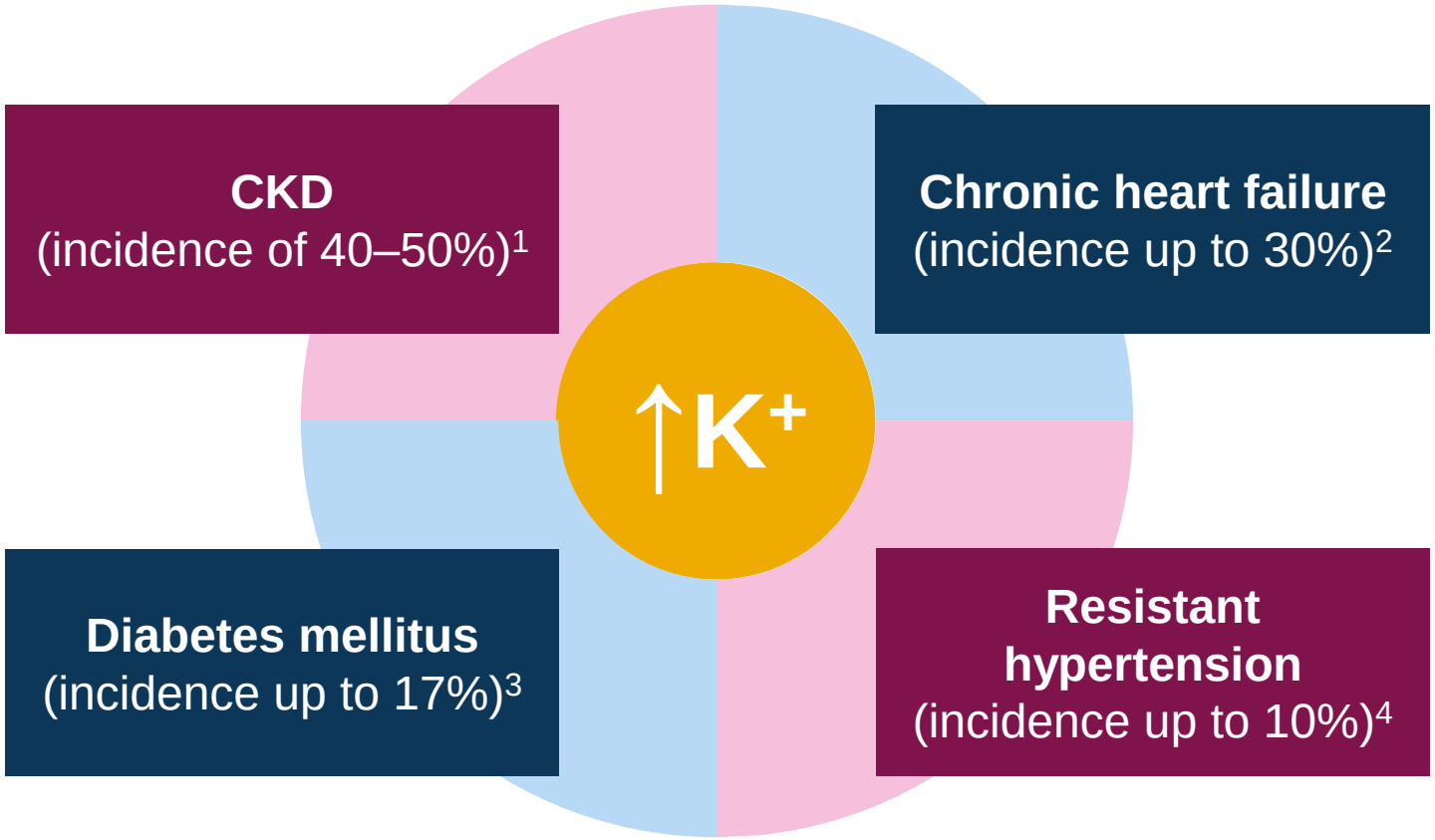
- Acute or chronic?
- Background CKD

5.5 vs 6.0 mEq/L

- Need to distinguish between acute treatment and chronic treatment/management

Acute:	Chronic:
• Cell membrane “stabilization”	Dietary interventions
• Reduction of Serum [K+]	Risk factor exposure management
• Redistribution into cells	Decreased uptake through GI tract
• Elimination from the body	Increased excretion (GI, kidney)

Patients with chronic diseases are at risk of developing hyperkalaemia

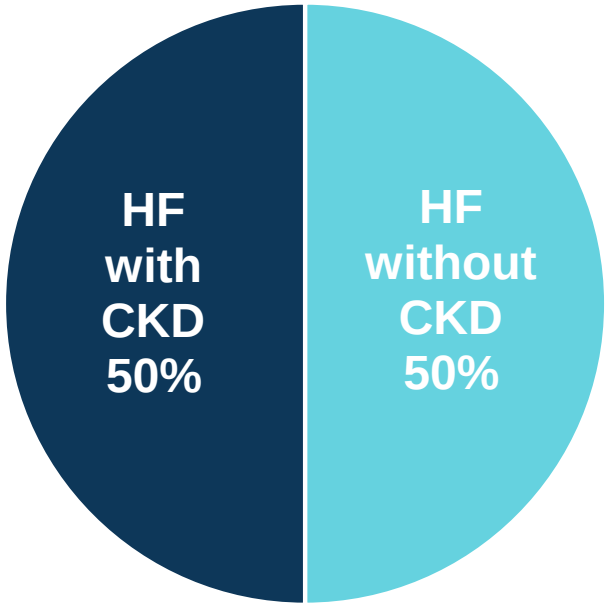


CKD, chronic kidney disease; K^+, potassium ion

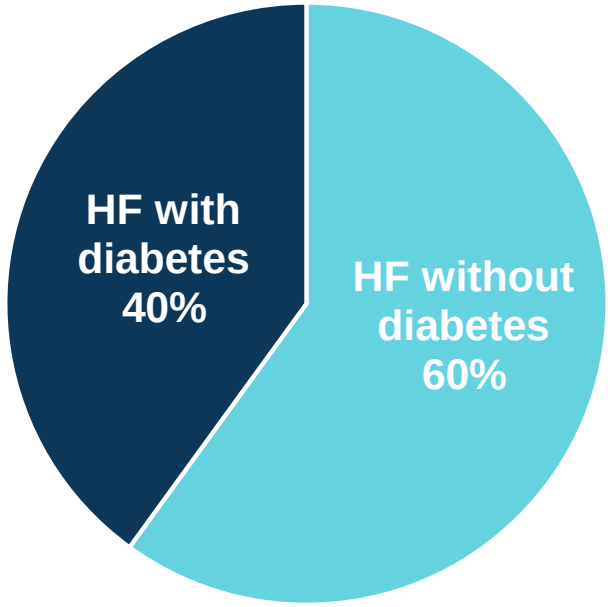
1. Kovesday CP. *Nat Rev Nephrol* 2014;10:653–62; 2. Vardeny O *et al*. *Circ Heart Fail* 2014;7:573–9; 3. Nilsson E *et al*. *Int J Cardiol* 2017;245:277–84;
4. Chang AR *et al*. *Hypertension* 2016;67:1181–8.

Conditions associated with hyperkalaemia often co-exist

Up to **~50%** of patients with HF also have CKD



Diabetes is present in **~40%** of patients hospitalised for acute HF

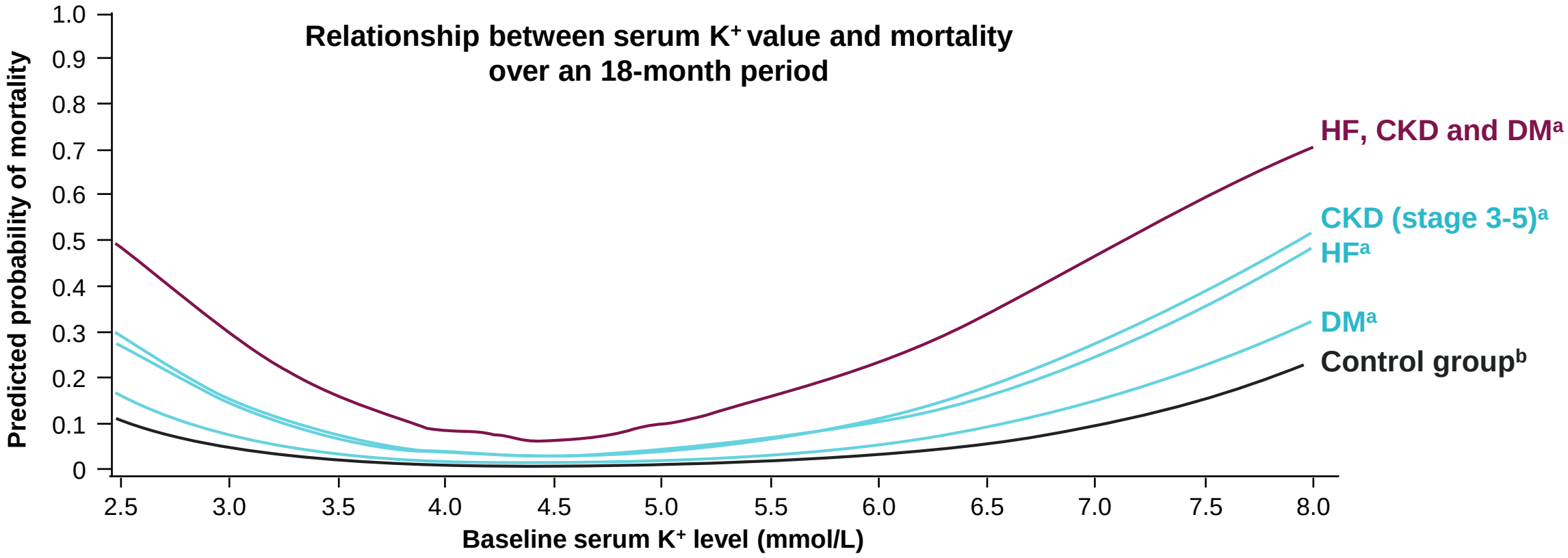


CKD, chronic kidney disease; HF, heart failure

Aguilar D. *Circ Heart Fail* 2016;9:e003316.

Hyperkalemia associated mortality was higher with comorbidities

Analysis of electronic medical record data from multiple US integrated health delivery networks of 911,698 patients with ≥2 potassium measurements between 2007 and 2012



[a]Signficant vs. control group; [b]Control group comprised of individuals without known HF, CKD, DM, CVD, or HTN.

CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; HF = heart failure; HTN = hypertension; US = United States.

Collins AJ et al. *Am J Nephrol.* 2017;46:213–221.

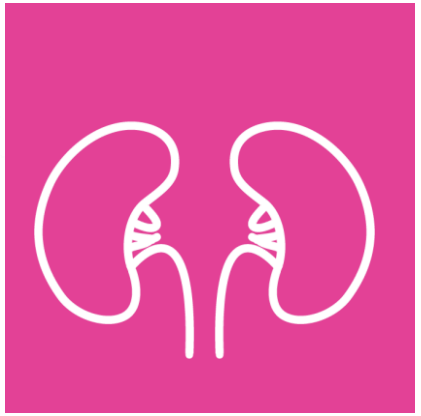
Hyperkalaemia can occur due to diet, drugs, or diseases

DIET

- Increased dietary intake of K^+
- Salt substitutes

DRUGS*

- RAAS inhibitors
- NSAIDs
- β-blockers
- Diuretics



DISEASES*

- Chronic kidney disease
- Heart failure
- Diabetes mellitus
- Resistant hypertension

*Inclusive of, but not limited to, these diseases

K^+, potassium ion; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin–angiotensin–aldosterone system

Hollander-Rodriguez J, Calvert JF Jr. Am Fam Physician 2006;73:283–290

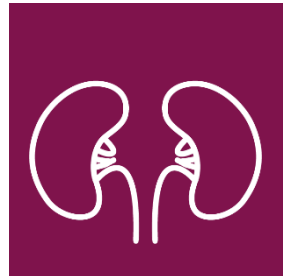
Class	Mechanism	Example
ACEi	Inhibit conversion of angiotensin I to angiotensin II	Captopril, lisinopril, perindopril, etc.
ARB	Inhibit activation of angiotensin I receptor by angiotensin II	Losartan, irbesartan, candesartan, etc.
Aldosterone antagonist	Block aldosterone receptor activation	Spironolactone, eplerenone, and finerenone
β-Adrenergic receptor blocker	Inhibit renin release	Propranolol, metoprolol, and atenolol
Digitalis glycoside	Inhibit Na^+-K^+-ATPase, necessary for collecting duct K^+ secretion	Digoxin
Heparin	Reduced production of aldosterone	Heparin sodium
Potassium-sparing diuretic	Block collecting duct apical Na^+ channel, decreasing gradient for K^+ secretion	Amiloride and triamterene
NSAIDs	Inhibit synthesis of prostaglandin E and prostacyclin, inhibiting renin release	Ibuprofen, naproxen, diclofenac, etc.
CNI	Inhibit Na^+-K^+-ATPase, necessary for collecting duct K^+ secretion	Cyclosporine and tacrolimus
ns-MRA	Block MR-mediated Na^+ reabsorption	Finerenone
Other	Block collecting duct apical Na^+ channel, decreasing gradient for K^+ secretion	Trimethoprim and pentamidine

Various classes of drugs are associated with hyperkalaemia

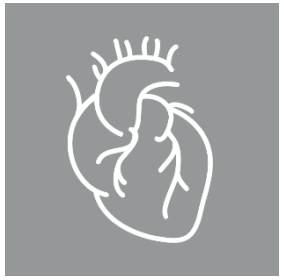
RAASi[1]

NSAIDs[1]

β-blockers[1]



Diuretics[1]



Valsartan/ sacubitril combination[2]

Calcineurin inhibitors: CyA and tacrolimus[1]

Heparin[1]

Antibiotics[1]

CyA, cyclosporin A; NSAID, non-steroidal anti-inflammatory drug; RAASi, renin-angiotensin-aldosterone system inhibitor

1. Hollander-Rodriguez J, Calvert JF Jr. *Am Fam Physician* 2006;73:283–90; 2. McMurray JJV *et al*. *N Engl J Med* 2014;371:993–1004.

RAASi therapy is recommended for the management of patients with CKD

NDD-CKD patients without diabetes mellitus

- KDIGO recommends that an ARB or ACEi be used in non-diabetic adults with NDD-CKD and urine albumin excretion >300 mg per 24 hours (or equivalent) in whom treatment with BP-lowering drugs is indicated (*1B*)

NDD-CKD patients with diabetes mellitus

- KDIGO recommends that an ARB or ACEi be used in adults with diabetes and NDD-CKD with urine albumin excretion >300 mg per 24 hours (or equivalent) (*1B*)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; NDD-CKD, nondialysis-dependent chronic kidney disease; RAASi, renin–angiotensin–aldosterone system inhibitor

Kidney Disease Improving Global Outcomes CKD Work Group. *Kidney Int Suppl* 2012;2:337–414

2018 ESC expert consensus report: Management of hyperkalaemia in patients with CV disease treated with RAASi therapy

Flow diagram on the management of hyperkalaemia in patients with indication for RAASi therapy

Is patient on maximal tolerated guideline-recommended target dose of RAAS inhibitor therapy?

Patient's sK^+ level		
4.5–5.0 mEq/L (4.5–5.0 mmol/L)	NO	• Initiate/up-titrate RAASi therapy and closely monitor K^+ levels • If K^+ levels rise >5.0 mEq/L, initiate an approved K^+-lowering agent
>5.0–≤6.5 mEq/L (5.0–≤6.5 mmol/L)	NO	• Initiate an approved K^+-lowering agent • If K^+ levels <5.0 mEq/L are detected, up-titrate RAASi and closely monitor K^+ levels • Maintain K^+ lowering agent unless an alternative treatable aetiology for hyperkalaemia is identified
	YES	• May initiate treatment with a K^+-lowering agent • Closely monitor K^+ levels • Maintain K^+ lowering agent unless an alternative treatable aetiology for hyperkalaemia is identified
>6.5 mEq/L (>6.5 mEq/L)	YES or NO	• Discontinue/reduce RAASi therapy • May initiate treatment with a K^+-lowering agent as soon as K^+ levels >5.0 mEq/L • Closely monitor K^+ levels

CV, cardiovascular; ESC, European Society of Cardiology; RAASi, renin–angiotensin–aldosterone system inhibitor; sK^+, serum potassium

Adapted from: Rosano GMC, et al. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180–188

Selected recommendations on hyperkalaemia treatment from expert consensus documents on heart failure management


ESC European Society of Cardiology

CONSENSUS DOCUMENT

Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology

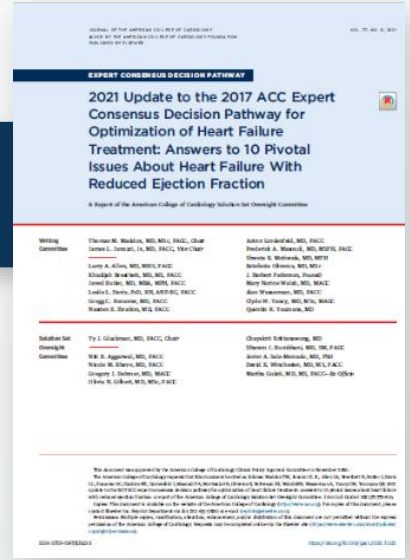
2019 ESC-HF Expert Consensus Document[1,a]

- [Novel oral K+ binders] may be considered in patients with HF with or without CKD to manage hyperkalaemia. In selected patients these therapies may enable use of MRAs and other RAASi in more patients and at higher doses, but it is not known whether this will improve patient outcomes

2021 ACC Expert Consensus Document[2,b]

- Abnormal renal function and/or hyperkalaemia are common barriers to initiation and titration of GDMT [in HF]. In patients with hyperkalaemia, education regarding a low K+ diet should be provided. In addition, novel K+ binders may be considered in patients with hyperkalaemia

Consider the use of novel K+ binders


EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

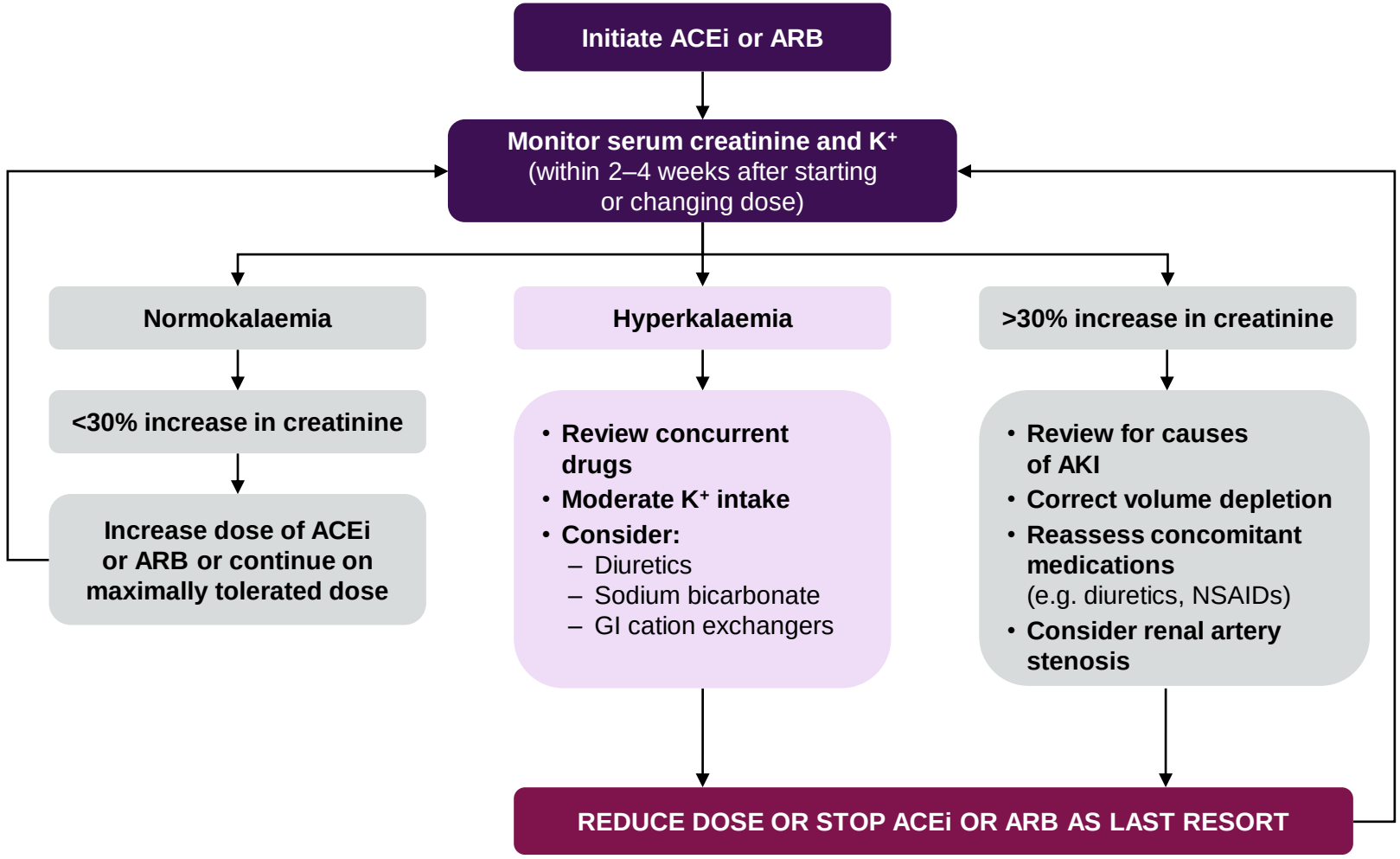
For full guidance, please refer to: 1. Seferovic PM et al. *Eur J Heart Fail* 2019;21:1169-1186; 2. Maddox TM, et al. *J Am Coll Cardiol* 2021;16;77:772–810
[a]Hyperkalaemia was not defined in the document;[1] [b]Hyperkalemia defined as serum K+ >5.0 mmol/L[2]
ACC, American College of Cardiology; CKD, chronic kidney disease; CV, cardiovascular; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; MRA, mineralocorticoid receptor antagonist; RAASi, renin-angiotensin-aldosterone system inhibitor
1. Seferovic PM et al. *Eur J Heart Fail* 2019;21:1169-1186; 2. Maddox TM, et al. *J Am Coll Cardiol* 2021;16;77:772–810

KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease

KDIGO Diabetes Work Group.
Kidney Int 2020;98(4S):S1–S115

Where might SZC fit?

KDIGO recommends managing hyperkalaemia by methods other than decreasing or stopping ACEi or ARB therapy



Note: ACEi or ARB should only be reduced or stopped after measures outlined above have failed
ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; GI, gastrointestinal; KDIGO, Kidney Disease: Improving Global Outcomes; NSAID, non-steroidal anti-inflammatory drug

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease

KDIGO Blood Pressure Work Group. *Kidney Int* 2021;99(3S):S1–S87

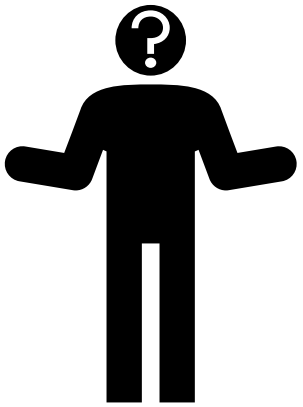
- "Strategies to control chronic hyperkalemia include dietary potassium restriction; discontinuation of potassium supplements, certain salt substitutes and hyperkalemic drugs; adding potassium-wasting diuretics, and oral potassium binders"
- "In CKD patients receiving RASi who develop hyperkalemia, the latter can be controlled with newer oral potassium binders in many patients, with the effect that RASi can be continued at the recommended dose"

Where might SZC fit?

Refer to KDIGO guidelines for more details and further practice points
CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; RASi, renin–angiotensin system inhibitor(s)

Therapeutic dilemma in managing hyperkalaemia while optimising RAASi therapy

RAASi therapy ⊷ – – – – – ⊷ **Hyperkalaemia**



Guidelines recommend optimising RAASi therapy[1–4,a]

RAASi improves outcomes

- Reduces CV morbidity and mortality[1–3]
- Slows CKD progression[4–5]

May prevent patients from **achieving target RAASi doses**[6]

Leads to **RAASi dose reduction or discontinuation and worse cardiorenal outcomes, including mortality**[6]

[a]ACCF/AHA, ACC/AHA/HFSA and ESC HF guidelines define RAASi therapy as ACEi, ARB, MRA and ARNi. KDIGO 2020 clinical practice guideline for diabetes management in CKD defines RAASi therapy as ACEi or ARB

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACEi, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; CV, cardiovascular; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; RAASi, renin–angiotensin–aldosterone system inhibitor

1. Ponikowski P, et al. *Eur Heart J* 2016;37:2129–2200; 2. Yancy CW, et al. *J Am Coll Cardiol* 2013;62:e147–e239; 3. Yancy CW, et al. *Circulation* 2017;136:e137–e161; 4. KDIGO Diabetes Work Group. *Kidney Int Suppl* 2020;98:S1–S115; 5. KDIGO Blood Pressure Work Group. *Kidney Int Suppl* 2012;2:337–4146; 6. Epstein M, et al. *Am J Manag Care* 2015;21(Suppl. 11):S212–S220

Recommendation 3.8.1: We suggest a nonsteroidal mineralocorticoid receptor antagonist with proven kidney or cardiovascular benefit for adults with T2D, an eGFR >25 ml/min per 1.73 m2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of RAS inhibitor (RASi) (2A).

Practice Point 3.8.1: Nonsteroidal MRA are most appropriate for adults with T2D who are at high risk of CKD progression and cardiovascular events, as demonstrated by persistent albuminuria despite other standard-of-care therapies.

Practice Point 3.8.2: A nonsteroidal MRA may be added to a RASi and an SGLT2i for treatment of T2D and CKD in adults.

Practice Point 3.8.3: To mitigate risk of hyperkalemia, select people with consistently normal serum potassium concentration and monitor serum potassium regularly after initiation of a nonsteroidal MRA (Figure 26).

Practice Point 3.8.4: The choice of a nonsteroidal MRA should prioritize agents with documented kidney or cardiovascular benefits.

Practice Point 3.8.5: A steroidal MRA may be used for treatment of heart failure, hyperaldosteronism, or refractory hypertension, but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among people with a low GFR.

Traditional HK treatment options are associated with limitations

Low-K^+ diet[1]

- Difficult to adhere to
- Limiting K^+-rich foods can cause constipation
- Contradicts DASH diet; may worsen chronic hypertension

Diuretics[1]

- Efficacy depends on residual renal function (until diuresis is present)
- Increased risk of gout and diabetes depending on choice of diuretic
- May produce volume contraction, decreased distal nephron flow, worsening of kidney function, and reduced K^+ excretion depending on choice of diuretic

Discontinuation or dose reduction of RAASi therapy[1]

- Stopping or suboptimal utilization of renal/ cardioprotective RAASi therapy

Traditional potassium binders (SPS)[2–4]

- No long-term efficacy has been evaluated
- Gastric irritation, anorexia, nausea, vomiting, constipation, and occasionally diarrhea may occur
- Hard, gritty texture and unpleasant taste may reduce palatability

DASH, Dietary Approaches to Stop Hypertension; HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor; SPS, sodium polystyrene sulfonate

1. Dunn J, et al. *Am J Manag Care* 2015;21:S307–S315; 2. Chaitman M, et al. *P T* 2016;41:43–50; 3. Sanofi-Aventis US LLC. Kayexalate US Prescribing Information 2018; 4. Zann V, et al. *Drug Des Devel Ther* 2017;11:2663–2673

Are we optimally managing patients with HK?

HK, hyperkalemia; RAASi, renin–angiotensin–aldosterone system inhibitor

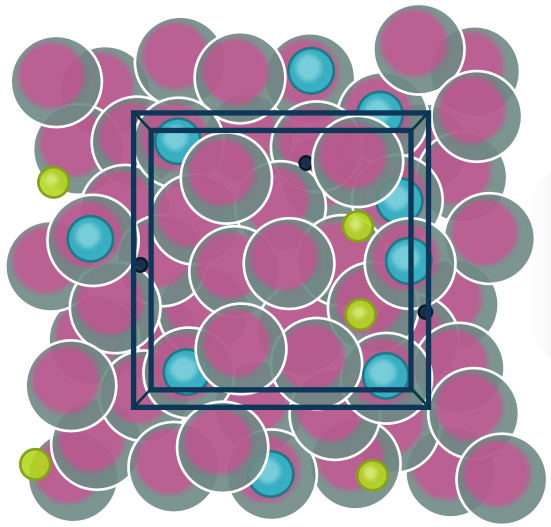
Selected characteristics of potassium binders

	SPS[1]	Patiromer[4]	SZC[6]
Approval date	1958[a]	USA: 2015; EU: 2017	USA: 2018; EU: 2019
Mechanism	Nonspecific sodium cation-exchange resin; may also bind calcium and magnesium	Nonspecific cation-binding in exchange for calcium	Highly selective; preferentially captures K^+ ions
Onset	1–2 hours	4–7 hours[5]	1 hour
Starting dose	15 g 3–4 times daily[2]	8.4 g once daily	For non-dialysis patients: 10 g three times daily (starting dose); 5 g once daily (maintenance)
Location	Colon[3]	Predominantly distal colon	Entire gastrointestinal tract

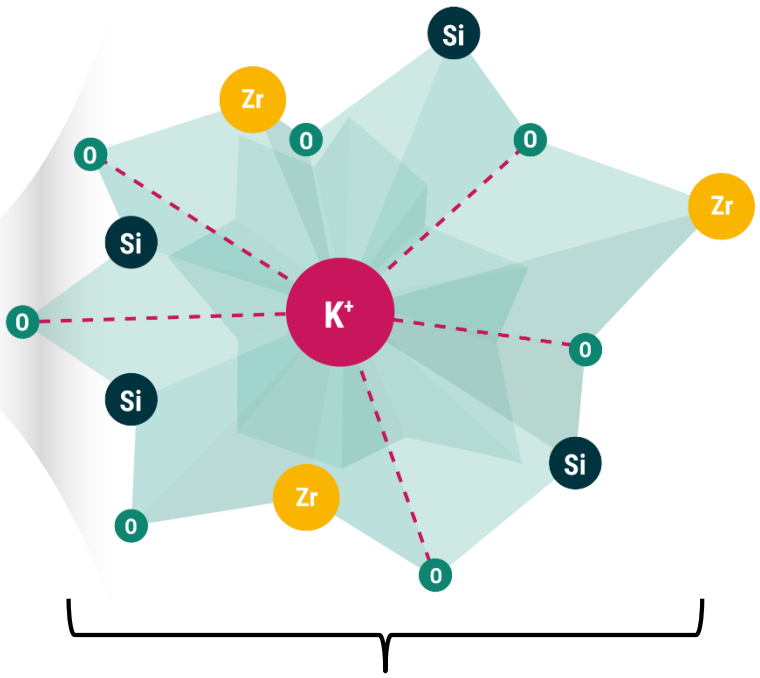
[a]SPS was FDA-approved prior to the Kefauver–Harris Drug Amendments in 1962, which required drug manufacturers' to prove effectiveness of their product[3]
FDA, US Food and Drug Administration; SPS, sodium polystyrene sulfonate
1. Chaitman M, et al. *P T* 2016;41:43–50; 2. Sanofi. Resonium A EU Summary of Product Characteristics 2019; 3. Sterns RH, et al. *J Am Soc Nephrol* 2010;21:733–735; 4. Garimella PS, Jaber BL. *Am J Kidney Dis* 2016;67:545–547; 5. Vifor Fresenius Medical Care Renal Pharma France. Veltassa (Patiromer) EU Summary of Product Characteristics 2018; 6. AstraZeneca AB. LOKELMA▼ EU Summary of Product Characteristics 2020

Sodium Zirconium Cyclosilicate crystal structure

SZC is indicated for the treatment of HK in adults[1]



Chemical formula:
$H_6Na_2O_9Si_3Zr^{+2}$



Average binding-site width: 3 Å

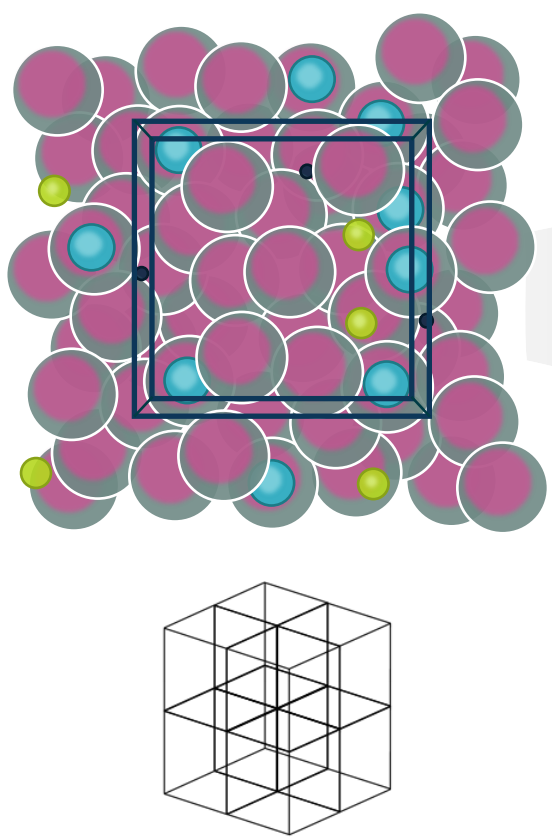
Key molecular characteristics:[1,3]

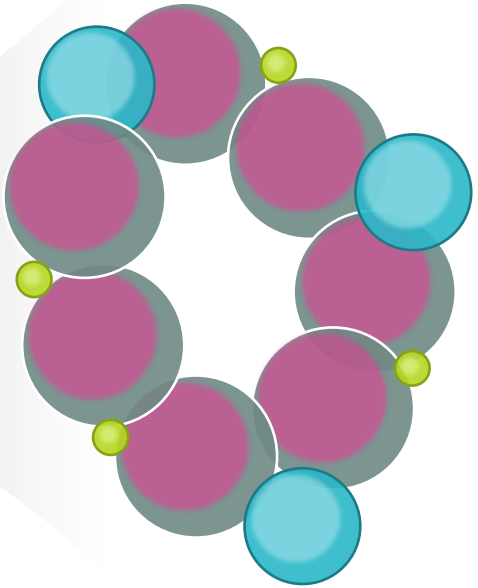
- Inorganic crystalline zirconium silicate compound
- Not a polymer
- Insoluble, highly stable, and does not expand in water
- Not systemically absorbed
- High affinity for K^+ [a]
- Exchanges Na^+ and H^+ for K^+

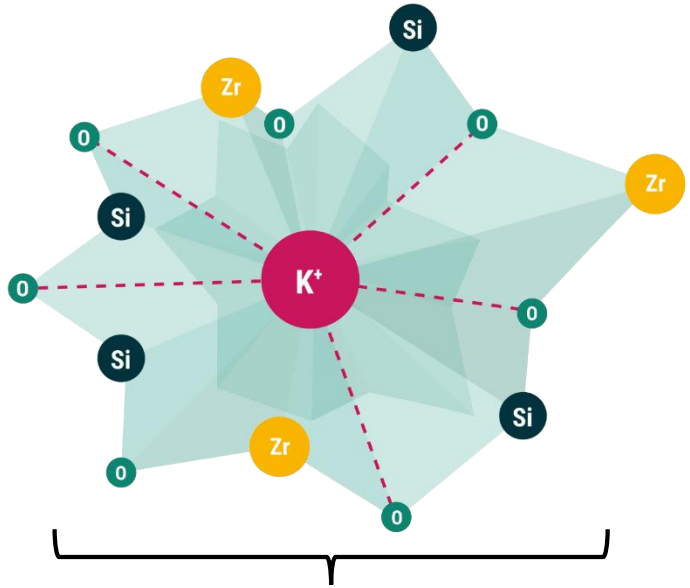
[a]In vitro activity does not always equate to clinical efficacy; images are illustrative only
HK, hyperkalemia
2. US National Institutes of Health National Center for Biotechnology Information PubChem Open Chemistry Database. Compound summary: sodium zirconium cyclosilicate (CID 91799284). Available at: https://pubchem.ncbi.nlm.nih.gov/compound/91799284#section=Top (Accessed June 2020); 3. Stavros F, et al. *PLoS One* 2014;9:e114686

SZC crystal structure

Cubic unit cell (space filled) → **7-member ring (space filled)** → **7-member ring (stick-and-ball figure)**





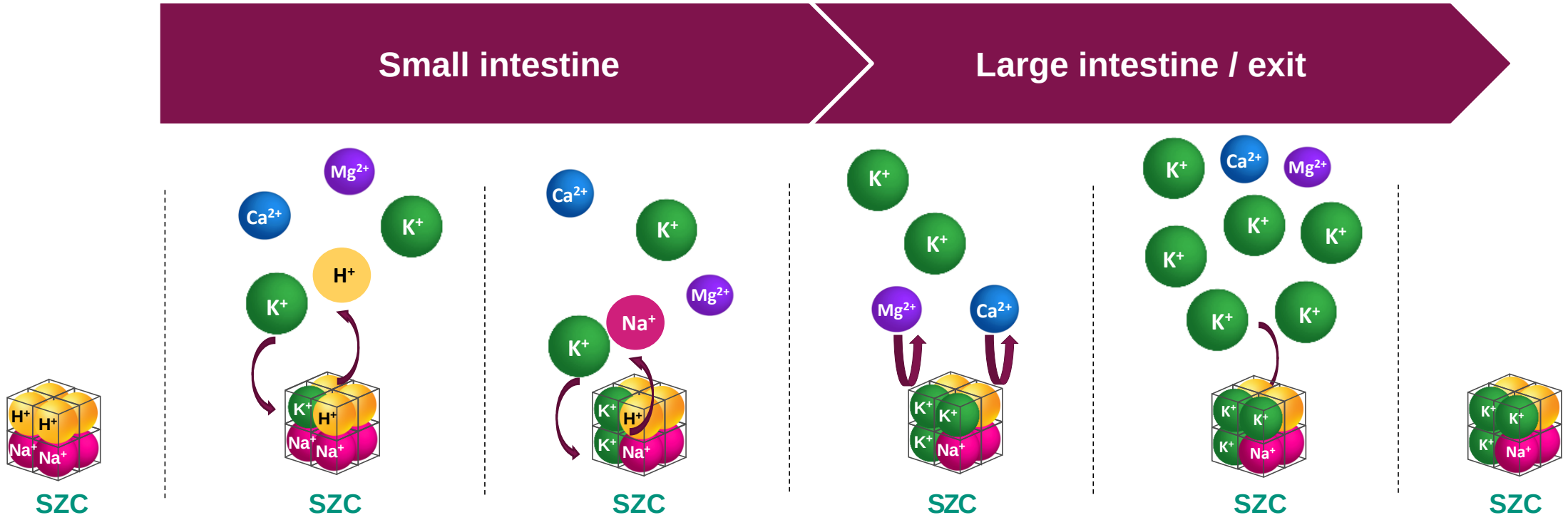


Average binding-site width: 3 Å

Individual squares/cubes represent one crystal

Stavros F, et al. *PLoS One* 2014;9:e114686

SZC binds K^+ throughout the GI tract[a]

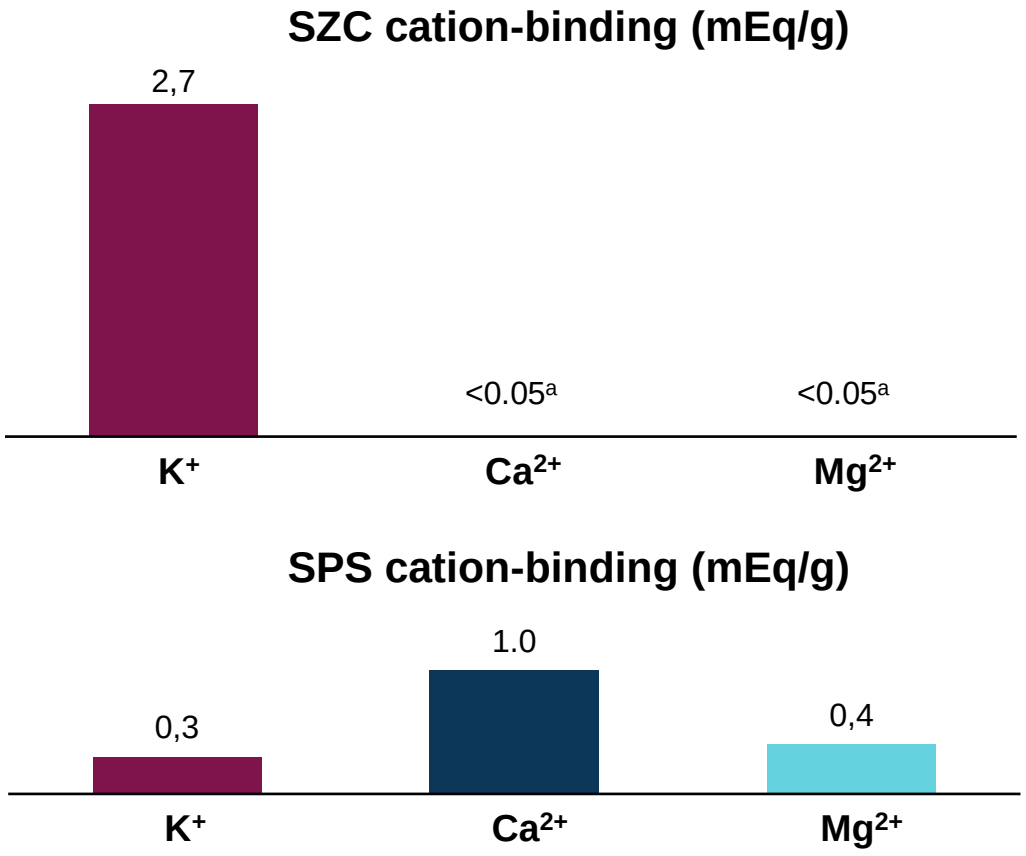


- Based on in vitro data, LOKELMA may begin working immediately in the small intestine to preferentially capture K^+
- K^+ is exchanged for sodium and hydrogen

[a]For illustrative purposes only
GI, gastrointestinal
Stavros F, et al. *PLoS One* 2014;9:e114686

SZC and SPS: Selectivity for K^+

- In vitro studies were designed to examine the ion exchange capacities of SZC and SPS
- K^+, Ca^{2+}, and Mg^{2+} concentration ratio of 1:1:1



- SZC displayed 9.3× more K^+-binding capacity than SPS
- SZC was >125× more selective for K^+ than SPS
- SPS was more selective for Mg^{2+} and Ca^{2+} than for K^+
- SZC and SPS have not been studied in head-to-head clinical trials and *in vitro* effects do not necessarily equate to efficacy, therefore no superiority of efficacy or other clinical benefit should be implied.

[a]Exchange capacity for Ca^{2+} and Mg^{2+} was <LOD (<0.05)
LOD, limit of detection; SPS, sodium polystyrene sulfonate
Adapted from: Stavros F, et al. *PLoS One* 2014;9:e114686

SZC: Clinical pivotal trial program overview

Study	Description
002 (N=90)	Phase 2, dose-escalating, safety, tolerability, and pharmacodynamics in acute mild HK (5.0–6.0 mEq/L) and CKD[1]
003 (N=753)	Phase 3, placebo-controlled RCT in mild-to-moderate HK (5.0–6.5 mEq/L), acute[2]
004 (N=258)	HARMONIZE: Phase 3, placebo-controlled RCT in HK (≥5.1 mEq/L)[3]; acute and maintenance phases (28 days and 11 months)[4]
005 (N=751)	Phase 3, open-label RCT in HK (≥5.1 mEq/L) assessing maintenance and long-term safety (up to 12 months)[5]
006 (N=196)	DIALIZE: Phase 3b, double blind, placebo-controlled RCT; reduce incidence of pre-dialysis HK with SZC[4]

SZC is indicated for the treatment of hyperkalemia in adult patients
Limitations of currently available clinical data include the following:[4]

- There is limited experience in patients with serum K^+ concentrations >6.5 mEq/L
- Clinical trials with SZC have not included exposure >1 year

CKD, chronic kidney disease; HK, hyperkalemia; RCT, randomized controlled trial
1. Ash SR, et al. *Kidney Int* 2015;88:404–411; 2. Packham DK, et al. *N Engl J Med* 2015;372:222–231; 3. Kosiborod M, et al. *JAMA* 2014;312:2223–2233; 4.LOKELMA EU Summary of Product Characteristics 2020; 5. Fishbane S, et al. Presented at American Society of Nephrology Kidney Week 2017; October 31st – November 5th, 2017; New Orleans, LA, USA; poster 005.

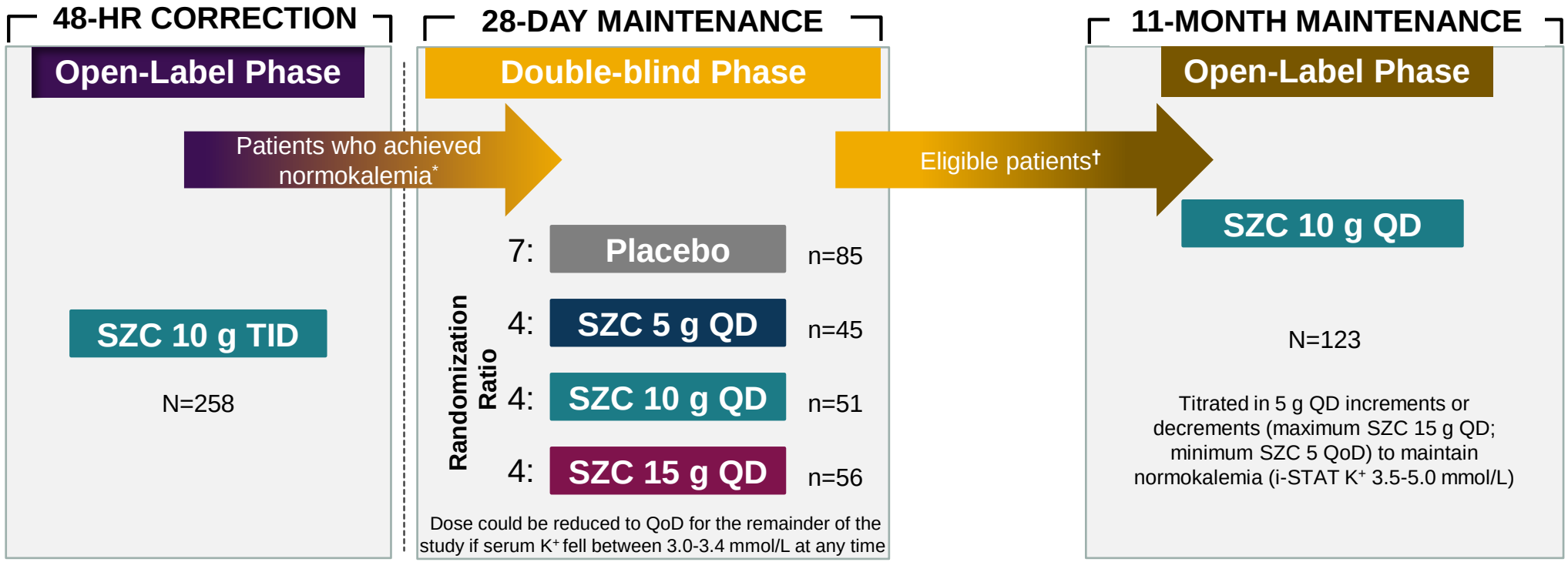
ZS-004 (HARMONIZE) + ZS-004E (Extension)
Study Designs

ZS-004[1]

Phase III, multicenter, 2-phase prospective study in patients with serum K^+ ≥5.1 mmol/L at 44 nephrology, cardiology, general research sites in US, South Africa, and Australia

ZS-004E (EXTENSION)[2]

Extension phase of patients who completed ZS-004 at 30 sites in US, South Africa, and Australia



*Proceeded to maintenance phase if patient achieved normokalemia (i-STAT K^+ 3.5-5.0 mmol/L) by morning of study Day 3; †Two patients with i-STAT K^+ >5.5 mmol/L at the end of ZS-004 entered the correction phase of ZS-004E where they received SZC 10 g TID with meals and proceeded to the 11-month maintenance phase within 1 day once normokalemia (i-STAT K^+ 3.5-5.0 mmol/L) was achieved. The remaining patients with i-STAT K^+ 3.5-5.5 mmol/L at the end of ZS-004 immediately entered the 11-month maintenance phase to receive SZC 10 g QD.

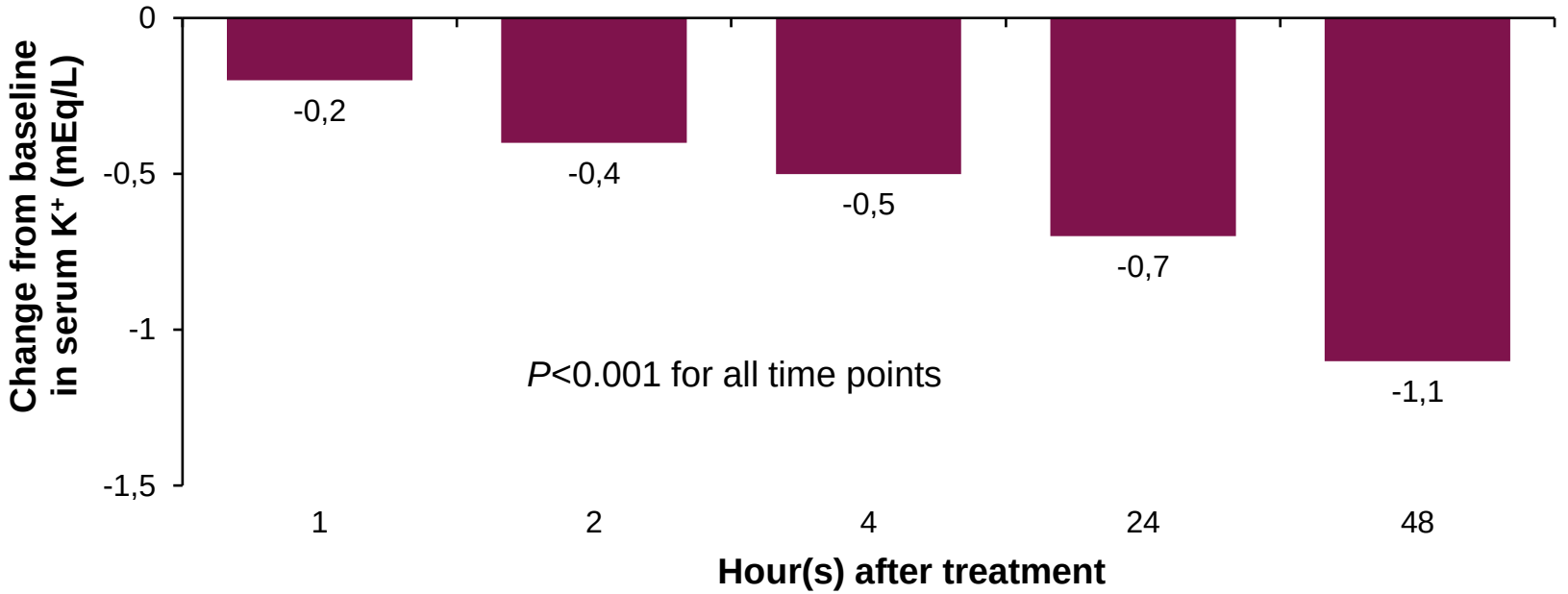
QoD = every other day; RAASi = renin–angiotensin–aldosterone system inhibitor; SZC = sodium zirconium cyclosilicate; US = United States.

1. Kosiborod M et al. Article and protocol. *JAMA*. 2014;312:2223-2233; 2. Roger SD et al. Article and supplementary material. *Am J Nephrol.* 2019;50:473-480.

SZC: Onset of action at 1 hour

- One dose of SZC significantly reduced (–0.2 mEq/L) serum K^+ levels **at 1 hour** vs baseline (*P*<0.001)[1,2]
- **88% of patients achieved normokalemia** during the 48-hour correction phase[2]
- The median time to serum K+ normalisation was 2.2 hours (interquartile range 1.1 to 22.3)[1]

Mean serum K^+ level with SZC 10 g three times daily for 48 hours (N=258)[1a]



Open-label phase mean baseline serum K^+: **5.6 mEq/L**

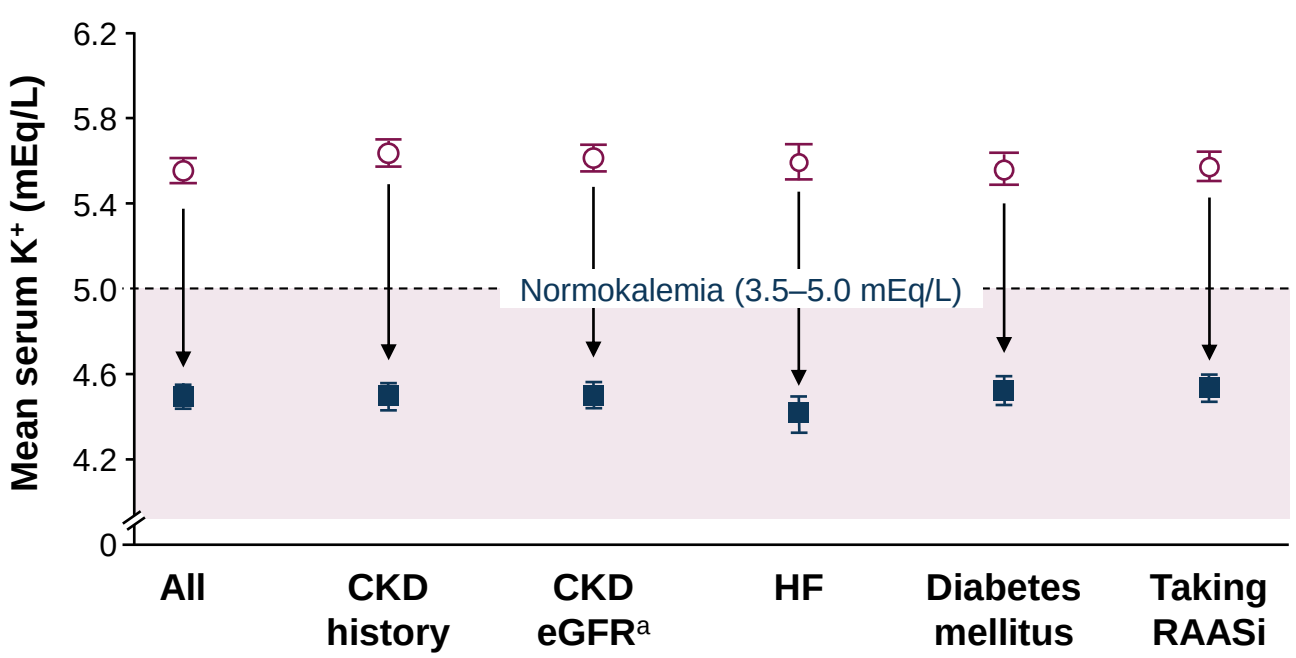
Comorbidities/treatment at baseline: CKD (60%), HF (11%), T2DM (66%),[3b] and RAASi use (70%)[1]

[a]In the open-label 48-h phase of the HARMONIZE trial; [b]Note: CKD, HF, and T2DM percentages have been updated based on revised definitions according to Medical Dictionary for Regulatory Activities[3]
CKD, chronic kidney disease; HF, heart failure; RAASi, renin–angiotensin–aldosterone system inhibitor; T2DM, Type 2 diabetes mellitus
1. Kosiborod M, et al. *JAMA* 2014;312:2223–2233; 2. LOKELMA EU Summary of Product Characteristics 2020

SZC reduced serum K^+ across patient types

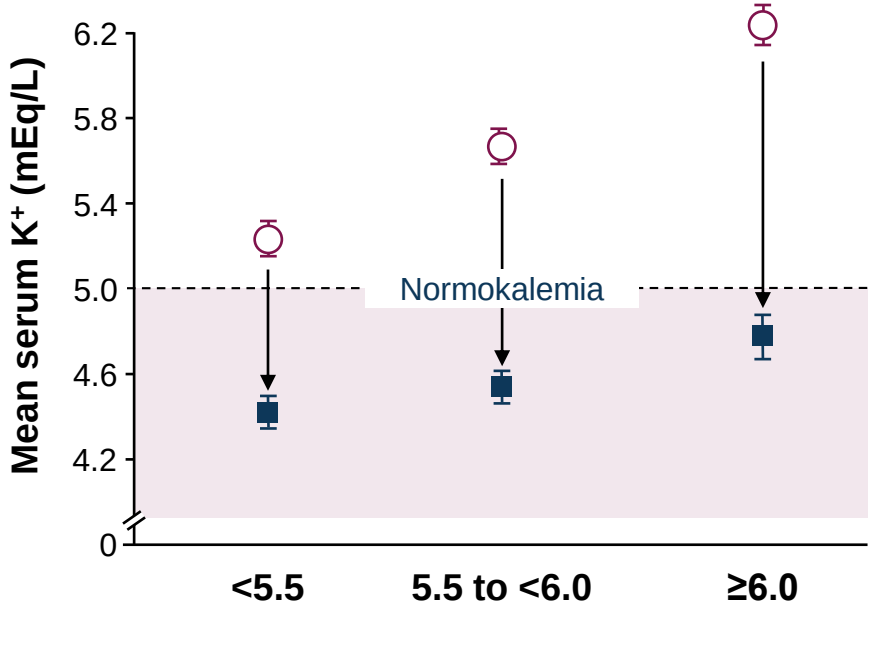
- SZC consistently reduced serum K^+, regardless of comorbidities, use of RAASi therapy, or baseline K^+ level[1]

Mean serum K^+ level at 0 and 48 hours across pre-specified subgroups[2]



Patient subgroups

No. of patients:						
○ Baseline	258	169	179	94	170	180
■ 48 hours	251	163	172	92	166	173



Baseline K^+ level (mEq/L)

No. of patients:			
○ Baseline	119	100	39
■ 48 hours	115	99	37

[a]<60 mL/min/1.73 m^2

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; RAASi, renin–angiotensin–aldosterone system inhibitor

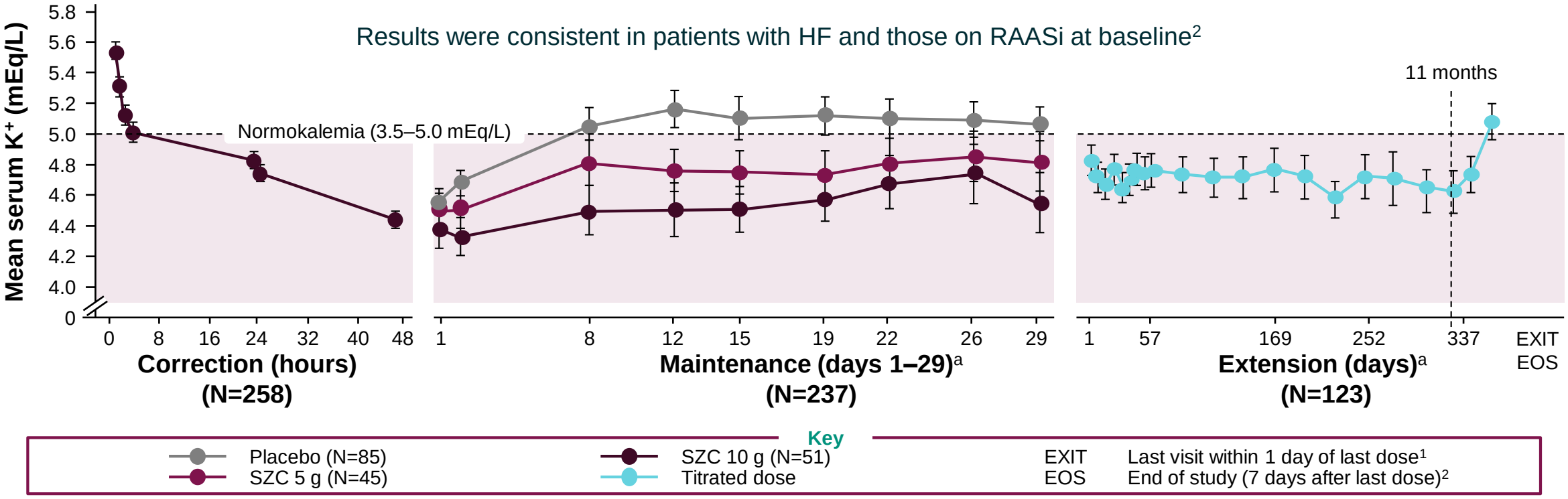
1. LOKELMA EU Summary of Product Characteristics 2020; 2. Adapted from: Kosiborod M, et al. *JAMA* 2014;312:2223–2233

SZC: Sustained K^+ control for up to 1 year

- 88% of patients receiving SZC maintained an average serum K^+ of <5.1 mEq/L over 11 months[1]
- No dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations[1]

Mean serum K^+ levels across correction, maintenance, and extension phases[1]

Results were consistent in patients with HF and those on RAASi at baseline[2]



Adapted from the SZC SmPC[1]

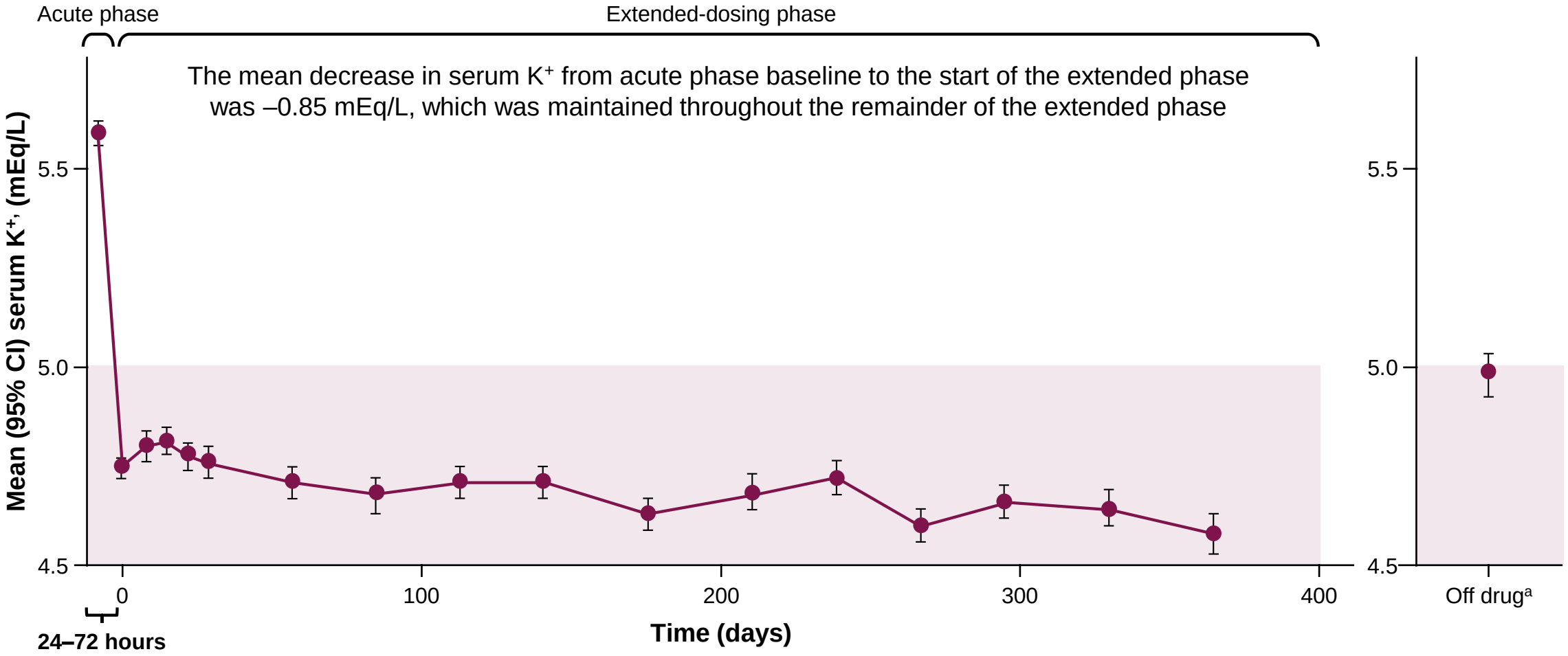
[a]Please note that the recommended starting dose for maintenance therapy with LOKELMA▼ for non-dialysis patients is 5 g QD, which may be titrated to 10 g QD as needed. No more that 10 g QD should be used for maintenance therapy. The 5-g QD dose can be downtitrated to 5 g QOD.[1] The extended maintenance group contained a small proportion (11%) of patients who were treated with SZC 15 g QD which is not a licensed maintenance dose in the EU except as a maintenance therapy in dialysis patients[1]

HF, heart failure; QD, once daily; QOD, every other day; RAASi, renin–angiotensin–aldosterone system inhibitor

2. Kosiborod M, et al. *JAMA* 2014;312:2223–2233

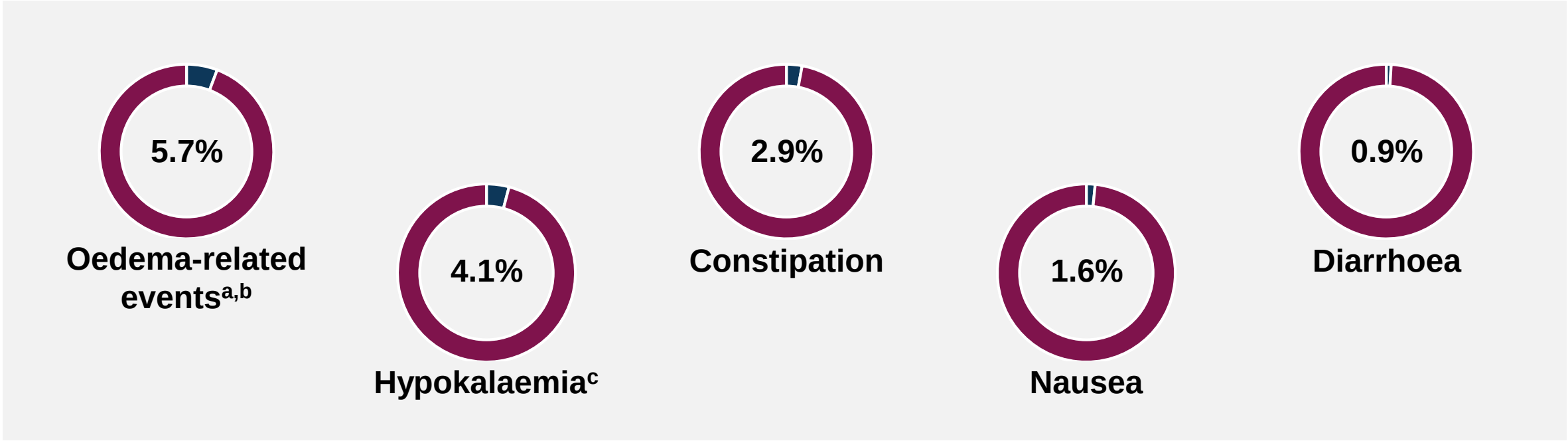
Study 005: Sustained K^+ control over 1 year

Adult outpatients (≥18 years) with HK (serum K^+ ≥5.1 mEq/L) were enrolled across 56 sites from the US, Australia, Germany, UK, Netherlands, Romania, and South Africa. No dietary restrictions or changes in RAASi were required.



P<0.001
[a]Off-drug values collected 7 (±1) days after the last administration of LOKELMA The extended maintenance group contained a small proportion (11.7%) of patients who were treated with 15 g QD, which is not a dose indicated for use in the EU for non-dialysis patients.
CI, confidence interval; QD, once dailyAdapted from: Fishbane S, et al. Presented at American Society of Nephrology Kidney Week 2017; October 31st – November 5th, 2017; New Orleans, LA, USA; poster 005

Most frequent adverse events reported with SZC



- Oedema-related events[a] were more commonly seen in patients treated with SZC 15 g (observed in a clinical dose-titration study); the events were observed in the maintenance phase only
- Hypokalaemia[c] was resolved with dosage adjustment or discontinuation of SZC
- In adults, the recommended starting dose of LOKELMA is 10 g in the correction phase (typically 24–48 hours); in the maintenance phase the minimal effective dose is recommended, starting at 5 g once daily and titrating up to 10 g once daily or down to 5 g every other day. For patients on dialysis the recommended starting dose is 5 g daily on non-dialysis days and the dose may be adjusted in increments of 5 g up to 15 g daily on non-dialysis days

[a]Includes generalised and peripheral oedema; [b]In patients who developed oedema-related events, 47% were resolved without treatment and the remaining patients had diuretic initiated or dose adjusted; [c]Serum K^+ <3.5 mEq/L

2018 ESC expert consensus on the management of hyperkalaemia in patients with CV disease treated with RAAS inhibitors

Rosano GMC, et al. *Eur Heart J Cardiovasc Pharmacother* 2018;4:180–188

Where might SZC fit?

Management of hyperkalaemia in patients with indication for RAASi therapy

Patients	On RAASi[a] target dose[b]	Recommendation
Chronic or recurrent hyperkalaemia on RAASi therapy		• An approved K^+-lowering agent may be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L • Closely monitor K^+ levels • Maintain treatment unless alternative treatable aetiology is identified
Chronic or recurrent hyperkalaemia	No	• RAASi should be optimised and an approved K^+-lowering agent may be initiated as soon as confirmed K^+ levels are >5.0 mEq/L • Closely monitor K^+ levels • Maintain treatment unless alternative treatable aetiology is identified
K^+ levels of 4.5–5.0 mEq/L	No	• Initiate/uptitrate RAASi therapy and closely monitor K^+ levels • If K^+ levels rise >5.0 mEq/L, initiate an approved K^+-lowering agent
K^+ levels of >5.0–≤6.5 mEq/L	No	• Initiate an approved K^+-lowering agent • If K^+ levels <5.0 mEq/L are detected, uptitrate RAASi and closely monitor K^+ levels • Maintain K^+-lowering agent unless an alternative treatable aetiology for hyperkalaemia is identified
	Yes	• May initiate treatment with a K^+-lowering agent • Closely monitor K^+ levels • Maintain K^+-lowering agent unless an alternative treatable aetiology for hyperkalaemia is identified
K^+ levels of >6.5 mEq/L	Yes or No	• Discontinue/reduce RAASi therapy • May initiate treatment with a K^+-lowering agent as soon as K^+ levels >5.0 mEq/L • Closely monitor K^+ levels

Adapted from Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: Coordinated by the Working Group on Cardiovascular Pharmacotherapy of the ESC;
[a]Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists; [b]Maximally tolerated guideline-directed dose
CV, cardiovascular; ESC, European Society of Cardiology; RAAS(i), renin–angiotensin–aldosterone (inhibitor)

Guidelines State HK can be Managed With K^+ Lowering Agents. Managing HK may Enable Guideline-recommended RAASi Therapy[1,2]

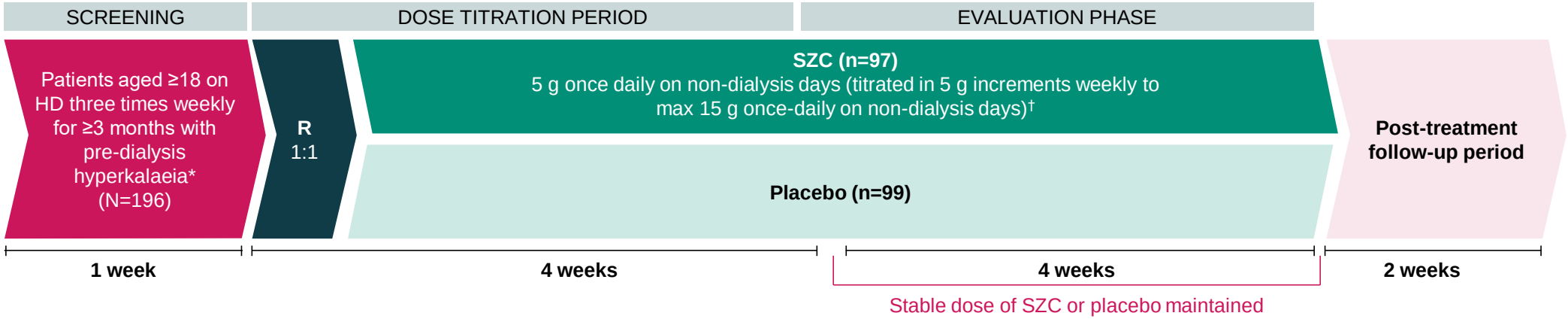
2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic HF[1]	2022 AHA/ACC/HFSA Guideline for the Management of HF[2]
Administration of K^+ lowering agents to treat hyperkalemia. By treating hyperkalemia, it may allow RAASi[a] initiation or uptitration in a larger proportion of patients In patients with chronic or recurrent hyperkalemia on RAASi[a] therapy: • RAASi[a] should be optimized when K^+ levels are <5.0 mEq/L • An approved K^+ lowering agent may be initiated as soon as K^+ levels are confirmed as >5.0 mEq/L. Closely monitor K^+ levels • Maintain K^+ lowering treatment unless treatable etiology for hyperkalemia is identified	In patients with HF who experience hyperkalemia (serum K^+ ≥5.5 mEq/L) while taking a RAASi[b], K^+ binders can be used to help manage hyperkalemia

[a]RAASi therapy includes ACEi, ARNI, and MRA. ARBs can be used if intolerant to ACEi or ARNI;[1] [b]RAASi therapy includes ACEi, ARB, ARNI, and MRA (spironolactone or eplerenone).[2]

1. McDonagh TA et al. Article and supplementary data. *Eur Heart J.* 2021;42(36):3599-3726; 2. Heidenreich PA et al. *J Am Coll Cardiol.* 2022;79(17):e263-e421.

PIVOTAL TRIAL DESIGN: DIALIZE

- The first-ever, double-blind, randomised, placebo-controlled trial in haemodialysis patients with hyperkalaemia[1]
- The safety and efficacy profile has been studied in 196 patients with end-stage renal disease on stable dialysis for at least 3 months[1]



PRIMARY ENDPOINT[1]

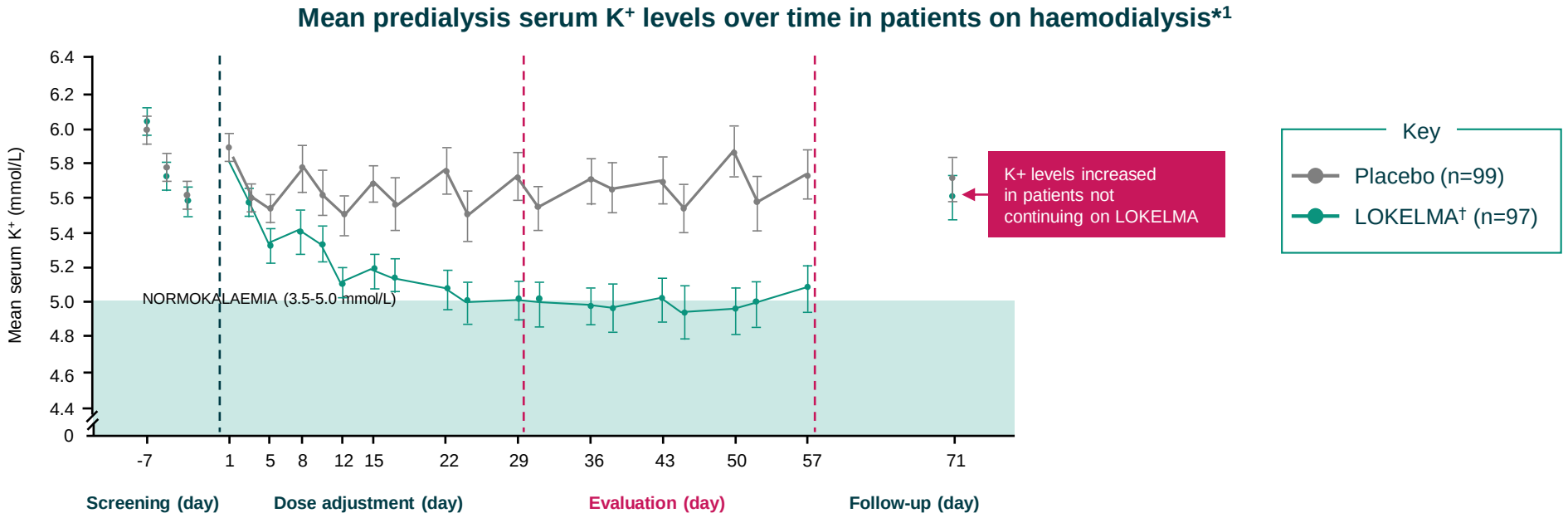
- Proportion of patients who maintained predialysis serum K^+ 4.0-5.0 mmol/L during at least three of four HD treatments following the long interdialytic interval and who did not require urgent rescue therapy during the 4-week evaluation phase

SECONDARY ENDPOINTS INCLUDED[1]

- Proportion of patients requiring any urgent rescue intervention

*Predialysis central laboratory serum K^+ ≥5.5 mmol/L after the LIDI and 5.1 mmol/L after at least one short interdialytic interval.[2]
†During the first 4 weeks of the treatment period, the LOKELMA and placebo doses were adjusted if the predialysis i-STAT serum K^+ after the LIDI was >5.0 mmol/L (one weekly dose adjustment). If the predialysis i-STAT serum K^+ was <4.0 mmol/L, dialysate K^+ concentration was increased by 0.5 or 1.0 mmol/L according to standard of care; if local practice did not include increasing dialysate K^+ concentrations or if the dialysate K^+ concentration could not be increased further, the LOKELMA or placebo dose could be reduced by 5 g or held if already dosed at the minimum dose of 5 g. If during the initial 4 weeks, the dose of LOKELMA or placebo was reduced or held and the predialysis i-STAT serum K^+ after the next LIDI was >5.0 mmol/ L, every effort was made to increase the dose by 5 g or restart 5 g if it was held.[1]
HD, haemodailysis; LIDI, long interdialytic interval; R, randomisation.
1. Fishbane S, Ford M, Fukagawa M, et al. *J Am Soc Nephrol*. 2019;30(9):1723-1733.

SZC REDUCED K+ LEVELS AND SUSTAINED K+ CONTROL IN HAEMODIALYSIS PATIENTS



- 41% (n=40/97) of patients achieved 4.0-5.0 mmol/L (vs 1% for placebo [n = 1/99]) in at least three of four haemodialysis sessions following the long interdialytic interval, without need for rescue therapy.[2]

*DIALIZE, a Phase III, multicentre, placebo-controlled study in 196 patients with end-stage renal disease on stable dialysis for at least 3 months and persistent pre-dialysis hyperkalaemia.
Double-blind, randomised phase: LOKELMA 5 g or placebo once daily on non-dialysis days. The dose could be adjusted weekly in 5 g increments up to 15 g once daily. Primary endpoint: proportion of patients who maintained a pre-dialysis serum K^+ between4.0 and 5.0 mmol/L on at least three out of four dialysis treatments after the long interdialytic interval and who did not receive rescue therapy during the evaluation period.[2]
†5 g once daily on non-dialysisdays (titrated in 5 g increments weekly to max 15 g once daily on non-dialysis days). The displayed error bars correspond to 95% confidence intervals.[1]
2. Fishbane S, Ford M, Fukagawa M, et al. J Am Soc Nephrol. 2019;30(9):1723-1733.

- Todays talk……
- Treatment options
- What about the foods?
- Sub-optimal RAASi and MRA therapy due to fear of hyperkalemia
- What is on the horizon to lower potassium?
- Unmet need of hyperkalemia in CKD: How would you manage the patient?

- Dietary measures
- Restrict their intake of high-potassium foods
- (>250 mg (6mmol) per 100 g)

- Maintain a low-potassium diet (potassium
- intake of ≤3 g per day)

- Lowering Potassium Levels
- It’s not all about bananas…
- Anyone can lower a patient’s potassium, the dietitian’s role, is to assess a patient’s diet and negotiate changes while:
  i. meeting patients’ preferences
  ii. keeping the diet healthy
  iii. maintaining safe potassium levels
- The hospital low potassium diets are very limiting

- Potassium:
- 1mmol = 39mg

	mmol potassium
Banana	***9***
Mandarin	***3***
Orange	***5***
Tomato (3 slices)	***3***
Mango (1 cheek)	***5***
Nectarine	***9***
Peach	***7***
Grapes	***6***
Mashed potato	***10***
Hot chips (small)	***12***
Juice (250mL)	***10***
Milkshake (250mL)	***10***
Ice-coffee (250m L)	***10***
Crisps (small packet)	**15**
Apple	***4***
Pear	***4***
Strawberries	***5***
Watermelon	***6***
Carrot (1/2 cup)	***4***
Beans (1/2 cup)	***1***
Zucchini (1/2 cup)	***4***

- What is the normal potassium intake?
- 1.30-50mmol/d
- 2.50-75mmol/d
- 3.75-100mmol/d
- 4.100-150mmol/d
- 5.Don’t know!

- What is the normal potassium intake?
- 75-100mol/L
- How do you assess potassium intake?

Plant-based foods

Absorption rate
50%–60%

Plant-based foods may have low absorption rate, net alkalizing effect, and carbohydrate content encourages K^+ shifts into intracellular space, minimizing impacts on serum K^+

Animal-based foods

Absorption rate
70%–90%

Animal-based protein has higher absorption and net acid effect results in higher amounts of K^+ remaining in serum

Processed foods

Absorption rate
90%

Potassium salts (often found in processed foods) absorption rate has been reported to be 90%

Figure 33 | Potassium absorption rates of plant-based, animal-based, and processed foods. Data from Picard K, Griffiths M, Mager DR, Richard C. Handouts for low-potassium diets disproportionately restrict fruits and vegetables. *J Ren Nutr*. 2021;31:210–214.[592]

Table 2| Summary of evidence and future research recommendations for dietary potassium in CKD

What we know		Future research
K ' -rich diets are consistent with fruit and vegetable-rich healthy dietary patterns. K' supplementation, at a general population level reduces blood pressure and lowers the risk of stroke. In people with CKD, estimations of dietary K' correlate poorly with	circulating K . Generalized dietary K* restriction in people with CKD may deprive them from other beneficial effects and nutrients of K' -rich diets. Investigate the effect of dietary K*	restriction in CKD on circulating levels Investigate the effect of fruit- and vegetable-rich diets in CKD Develop new methods and validate existing methods to estimate dietary K' intake in people with CKD Evaluate the impact of dietary K on serum concentration in people with CKD Evaluate the effects of dietary K restriction in people with CKD on clinically important outcomes, induding harms Evaluate the effects of unrestricted fruit/vegetable intake on the risk of hyperkalemia in people with advanced CKD or who are undergoing dialysis

- dietary potassium in patients with CKD was lacking; however, we did not find evidence that increased potassium intake, or liberalization of potassium restrictions, in patients with advanced CKD is safe. While we acknowledge that dietary potassium restriction is a valid strategy to treat acute hyperkalemia, we hypothesize that potassium restriction as a general strategy to prevent hyperkalemia in persons with CKD may deprive patients of the beneficial effects associated with potassium-rich diets. We recommend that interventional trials be conducted to clarify optimal dietary potassium advice for patients with

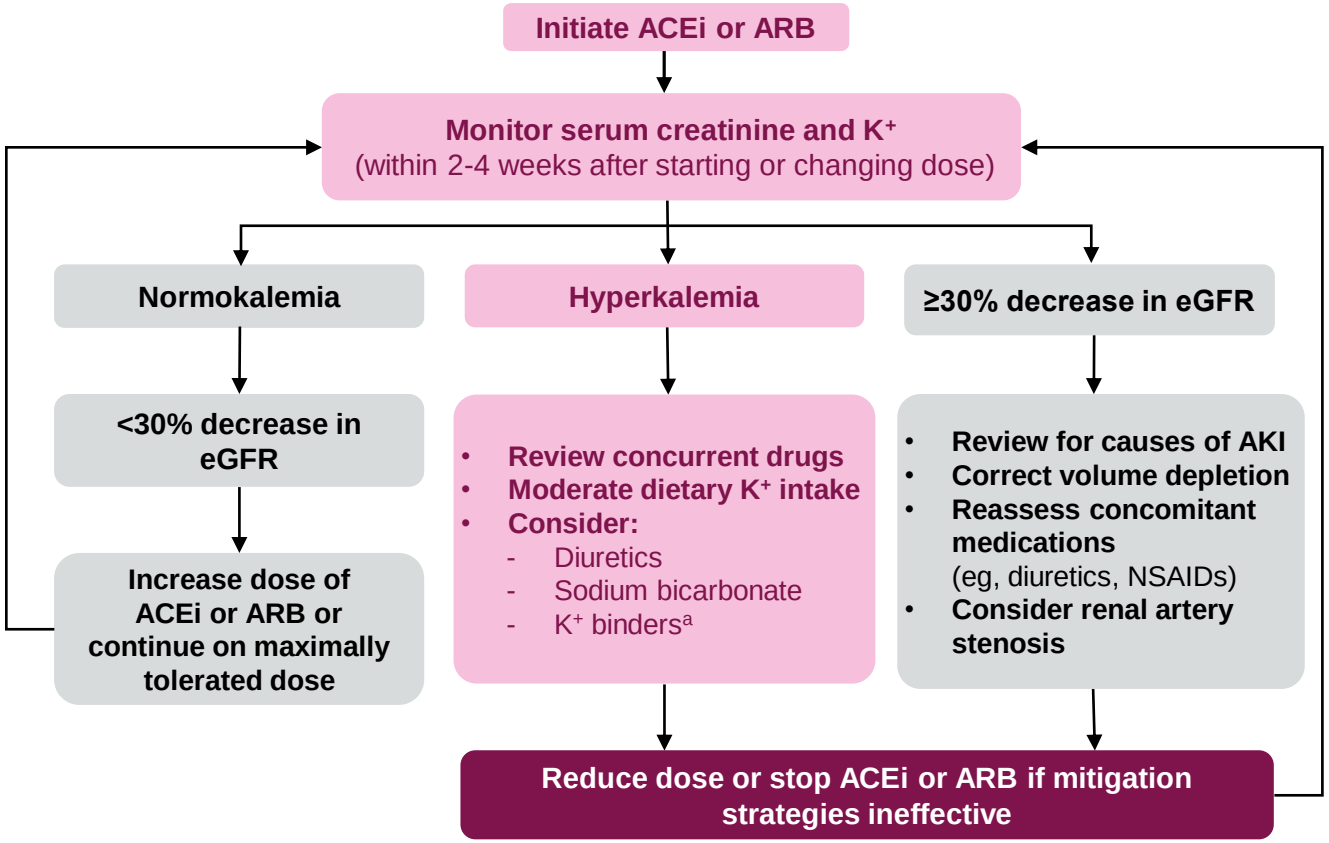
A Delphi Consensus Project to Capture Experts' Opinion on Hyperkalemia Management across the Cardiorenal Spectrum

A steering committee of nephrologists and cardiologists developed 37 statements. An online questionnaire completed by 32 experts in cardiorenal management in Greece. Median score used to determine the level of agreement and Disagreement Index (DI) used to determine the level of consensus for each statement.

This DELPHI project pointed out nephrologists' and cardiologists' agreement on hyperkalemia management in cardiorenal patients, thus it can help a cross-specialty optimal management of cardiorenal patients, with hyperkalemia not being an obstacle for disease modifying therapy.

The KDIGO 2024 CKD Guideline Provides a Stepwise Approach on Hyperkalemia Management in CKD

Algorithm for Monitoring Potassium and eGFR After ACEi/ARB Initiation



Actions to Hyperkalemia[b] Management in CKD

1st line: Address correctable factors

- Review non-RASi medications (e.g. NSAIDs, trimethoprim)
- Assess dietary potassium intake (dietary referral) and consider appropriate moderation of dietary potassium intake

2nd line: Medications

- Appropriate use of diuretics
- Optimize serum bicarbonate levels
- Licensed potassium exchange agents[c]

3rd line: Last resort

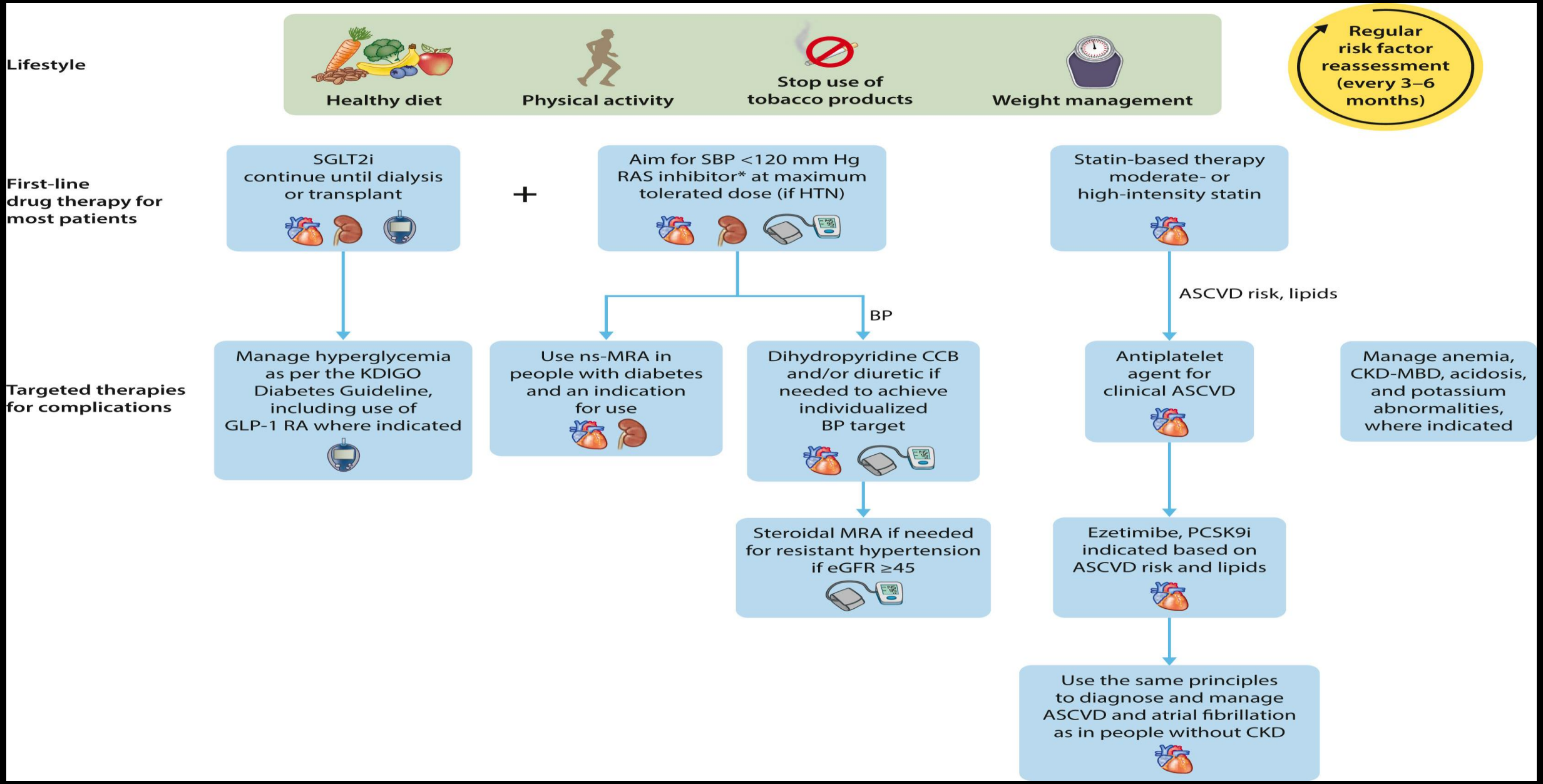
- Reduce dose or discontinue RASi/MRA (discontinuation is associated with increased cardiovascular events. Review and restart RASi or MRA at a later date if patient condition allows)

Note: RASi included ACEi or ARB.

[a]Such as SZC and patiromer; [b]Potassium >5.5 mmol/L; [c]SZC, patiromer, and sodium/calcium polystyrene sulfonates.

ACEi = angiotensin-converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonist; NSAIDs = nonsteroidal anti-inflammatory drugs; RASi = renin-angiotensin system inhibitor; SZC = sodium zirconium cyclosilicate.

KDIGO CKD Work Group. *Kidney Int.* 2024;105(Suppl 4S):S117-S314.



Kidney International 2024 105684-701DOI: (10.1016/j.kint.2023.10.016)

Safety and tolerability profile in clinical trials

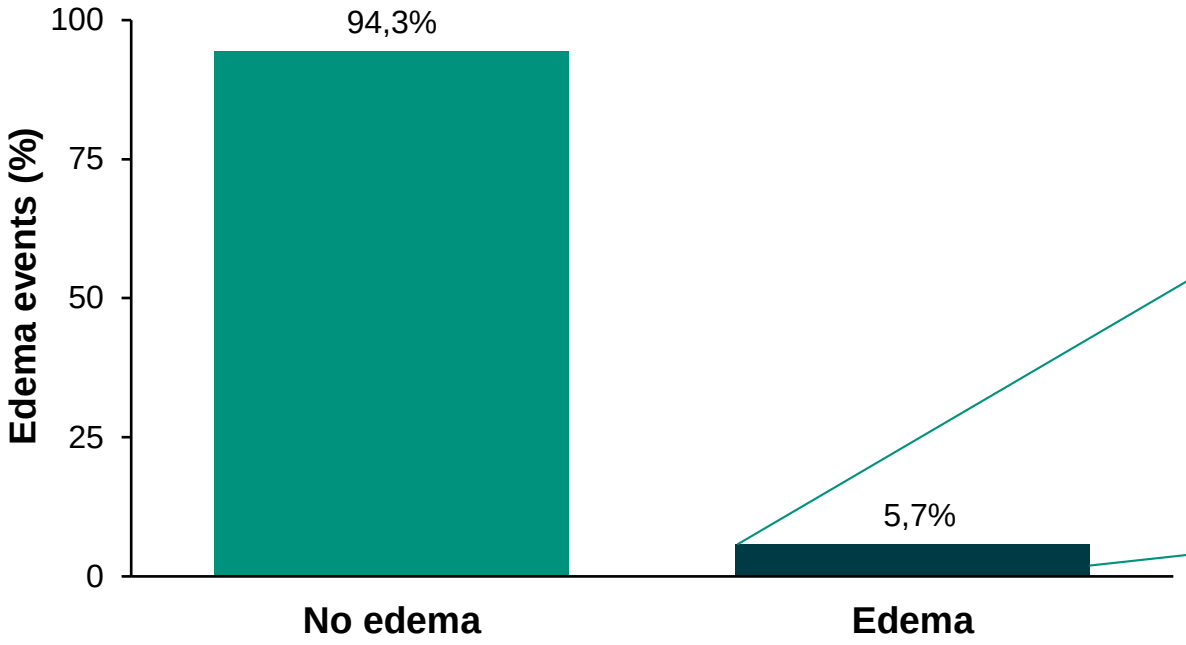
- 5.7% of patients receiving SZC reported edema-related events;[a] the events were more commonly seen in patients treated with 15 g. SZC 15-g dose is not approved for use in the EU
- No clinically significant changes in urinary sodium excretion, or serum magnesium and calcium levels, were observed with SZC
- 4.1% of patients receiving SZC developed hypokalemia (serum K^+ level <3.5 mEq/L), which resolved with dosage adjustment or discontinuation of SZC
- In a clinical drug–drug interaction study conducted in healthy individuals, co-administration of SZC with amlodipine, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan, or levothyroxine did not result in clinically meaningful drug–drug interactions
- SZC is not systemically absorbed or metabolized by the body
- SZC can transiently increase gastric pH, therefore it should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful pH-dependent bioavailability[b]
- SZC can be co-administered without spacing of dosing times with oral medications that do not exhibit pH-dependent bioavailability

SZC is not intended for use in place of emergency treatments; emergency treatment may require other temporary agents
[a]Includes generalized and peripheral edema
[b]Azole antifungals (ketoconazole, itraconazole, and posaconazole); anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, and rilpivirine); tyrosine kinase inhibitors (erlotinib, dasatinib, and nilotinib)

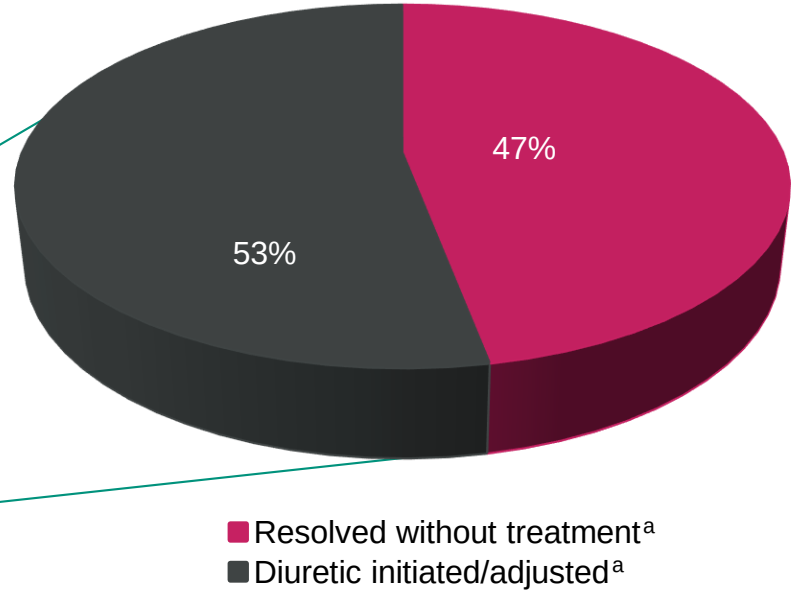
Edema-related events were mild-to-moderate and either resolved on their own or were easily managed with diuretics

- Edema-related events were reported by 5.7% of patients receiving SZC
- The events were observed in the maintenance phase only and were more commonly seen in patients treated with 15 g (15-g dose not recommended in the EU SmPC)

The rate of peripheral edema reported by patients



Of the 5.7% who presented with edema, approximately half were managed by initiating a diuretic or adjusting diuretic dose



[a]Some patients had multiple events so were counted more than once

MAINTENANCE DOSING[1]

- **SZC is a daily treatment option for hyperkalaemia (for non-dialysis patients)[1]**
- **Recommended dosing of SZC to achieve and sustain normokalaemia[1]**

FOR ADULT (NON-DIALYSIS) PATIENTS

Correction phase

3×  **/day[a,b]**

10 g
for 24 to 48 hours

until normokalemia is achieved[a,b]

Maintenance phase

1×  **/day[a,b]**

5 g
for up to 1 year

To establish minimum effective dose, SZC may be titrated
- Up to **10 g once daily** or
- Down to **5 g once every other day**

No more than **10 g once daily** should be used for maintenance therapy

New SmPC Update Based on DIALIZE Data

FOR HAEMODIALYSIS PATIENTS

RECOMMENDED STARTING DOSE

1×  **/non-dialysis days**

5 g

To establish normokalaemia, the dose may be titrated up or down weekly based on the predialysis serum K^+ after the long interdialytic interval

The dose could be adjusted at intervals of one week in increments of 5 g:
- **Up to 15 g once daily on non-dialysis days**

It is recommended to monitor serum K^+ weekly while the dose is adjusted. To maintain normokalaemia, it is recommended to monitor serum K^+ regularly (e.g., monthly or more frequently based on clinical judgement)

Serum K^+ levels should be monitored regularly during treatment. Monitoring frequency will depend upon a variety of factors, including other medications, progression of CKD and dietary K+ intake. If severe hypokalaemia should occur, SZC should be discontinued and the patient is re-evaluated.
SZC should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH-dependent bioavailability.

Serum K^+ levels should be monitored periodically during treatment
[a]If normokalaemia is not achieved within 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered; [b]Patients who miss a dose should be instructed to take the next usual dose at their normal time.[1] .

Oral Administration

- **SZC is a powder for oral suspension, available in 5 g or 10 g doses**
- **Mix SZC with 45 mL of water for oral administration[1]**

- ✓ Tasteless and odorless
- ✓ May be taken with many other medications and with or without food
- ✓ No special conditions for storage

Ensure patients stir well and drink suspension straight away while still cloudy (powder will not dissolve). Remind patients, if powder settles, to stir again before finishing drink[1]

SZC summary of key characteristics

SZC is indicated for the treatment of hyperkalemia in adults

	SZC
MOA	Preferential K^+-binding in exchange for sodium and hydrogen[1]
Onset of action	As early as 1 hour after the first dose[2]
Efficacy data	Acute treatment and maintenance data up to 1 year[2]
Drug–drug interactions	Should be administered at least 2 hours before or 2 hour after oral medications with clinically meaningful gastric pH-dependent bioavailability[2*]
Location of K^+-binding	Throughout GI tract[2]
Tolerability	Associated with:[2] • Hypokalemia • Edema-related events

There is limited experience in patients with serum potassium concentrations greater than 6.5 mEq/L[2]
*Examples of medicines that should be administered before or after LOKELMA include azole antifungals (ketoconazole, itraconazole, and posaconazole); anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, and rilpivirine); tyrosine kinase inhibitors (erlotinib, dasatinib, and nilotinib)
GI, gastrointestinal; MOA, mechanism of action
1. Garimella PS, Jaber BL. *Am J Kidney Dis* 2016;67:545–547;

Overall summary

SZC has the potential to improve management of hyperkalemia

- SZC has a rapid onset of action (as early as 1 hour of administration)[1,2]
- SZC provides sustained normokalemia, regardless of comorbidities or concomitant use of RAASi therapy[1,2]
- SZC is generally well tolerated and is a daily treatment option for hyperkalemia[1]

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